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☐ 1. Document ID: US 6255458 B1

L6: Entry 1 of 28 File: USPT Jul 3, 2001

US-PAT-NO: 6255458
DOCUMENT-IDENTIFIER: US 6255458 B1

TITLE: High affinity human antibodies and human antibodies against digoxin

DATE-ISSUED: July 3, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lonberg; Nils	Woodside	CA	N/A	N/A
Kay; Robert M.	San Francisco	CA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
GenPharm International	San Jose	CA	N/A	N/A	02

APPL-NO: 9/ 042353
DATE FILED: March 13, 1998

PARENT-CASE:
This application is a continuation-in-part of U.S. Ser. No. 08/758,417 filed Dec. 2, 1996, which is a continuation-in-part of U.S. Ser. No. 08/728,463 filed Oct. 10, 1996, which is a continuation-in-part of U.S. Ser. No. 08/544,404 filed Oct. 10, 1995, now U.S. Pat. No. 5,770,429, which is a continuation-in-part of U.S. Ser. No. 08/352,322 filed Dec. 7, 1994 now U.S. Pat. No. 5,625,126, which is a continuation-in-part of U.S. Ser. No. 08/209,741 filed Mar. 9, 1994, now abandoned which is a continuation-in-part of U.S. Ser. No. 08/165,699 filed Dec. 10, 1993, now abandoned which is a continuation-in-part of U.S. Ser. No. 08/161,739 filed Dec. 3, 1993, now abandoned which is a continuation-in-part of U.S. Ser. No. 08/155,301 filed Nov. 18, 1993 now abandoned, which is a continuation-in-part of U.S. Ser. No. 08/096,762 filed Jul. 22, 1993 now U.S. Pat. No. 5,814,318, which is a continuation-in-part of U.S. Ser. No. 08/053,131 filed Apr. 26, 1993, now U.S. Pat. No. 5,661,016 which is a continuation-in-part of U.S. Ser. No. 07/990,860 filed Dec. 16, 1992 now U.S. Pat. No. 5,545,806 which is a continuation-in-part of U.S. Ser. No. 07/904,068 filed Jun. 23, 1992 now abandoned, which is a continuation-in-part of U.S. Ser. No. 07/853,408 filed Mar. 18, 1992 now U.S. Pat. No. 5,789,650, which is a continuation-in-part of U.S. Ser. No. 07/834,539, filed Feb. 5, 1992, now U.S. Pat. No. 5,633,425, which is a continuation-in-part of U.S. Ser. No. 07/810,279 filed Dec. 17, 1991 now U.S. Pat. No. 5,569,825 which is a continuation-in-part of U.S. Ser. No. 07/575,962

filed Aug. 31, 1990 now abandoned, which is a continuation-in-part of U.S. Ser. No. 07/574,748 filed Aug. 29, 1990 now abandoned. This application also claims priority benefits under Title 35, United States Code, Section 120, to PCT Application No. PCT/US91/06185, filed Aug. 28, 1991, (which corresponds to U.S. Ser. No. 07/834,539 filed Feb. 5, 1992), PCT Application No. PCT/US92/10983, filed Dec. 17, 1992 PCT Application No. PCT/US94/04580, filed Apr. 25, 1994 PCT Application No. PCT/US96/16433, filed Oct. 10, 1996, and PCT Application No. PCT/US97/21803, filed Dec. 1, 1997.

INT-CL: [7] C07K 16/00
US-CL-ISSUED: 530/388.15; 530/388.9, 435/326
US-CL-CURRENT: 530/388.15; 435/326, 530/388.9
FIELD-OF-SEARCH: 424/175.1, 435/326, 435/346, 435/345, 530/388.9, 530/388.15

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
5567610	October 1996	Borrebaeck et al.	N/A

OTHER PUBLICATIONS

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Fishwild, et al. Nature Biotechnology. vol. 14, pp. 845-851, 1996.

ART-UNIT: 164
PRIMARY-EXAMINER: Chan; Christina Y.
ASSISTANT-EXAMINER: DiBrino; Marianne
ATTY-AGENT-FIRM: Townsend and Townsend and Crew LLP

ABSTRACT:

The invention relates to transgenic non-human animals capable of producing heterologous antibodies and methods for producing human sequence antibodies which bind to human antigens with substantial affinity.

2 Claims, 119 Drawing figures

☐ 2. Document ID: US 6232445 B1

L6: Entry 2 of 28 File: USPT May 15, 2001

US-PAT-NO: 6232445
DOCUMENT-IDENTIFIER: US 6232445 B1

TITLE: Soluble MHC complexes and methods of use thereof

DATE-ISSUED: May 15, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rhode; Peter R.	Miami	FL	N/A	N/A
Acevedo; Jorge	Miami	FL	N/A	N/A
Burkhardt; Martin	Miami	FL	N/A	N/A
Jiao; Jin-an	Fort Lauderdale	FL	N/A	N/A
Wong; Hing C.	Fort Lauderdale	FL	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Sunol Molecular Corporation	Miramar	FL	N/A	N/A	02

APPL-NO: 8/ 960190
DATE FILED: October 29, 1997

INT-CL: [7] C12P 21/08, C12N 15/09, A61K 39/00, A61K 39/385
US-CL-ISSUED: 530/387.3; 530/350, 530/395, 435/69.3, 424/185.1, 424/193.1, 424/192.1, 424/133.1
US-CL-CURRENT: 530/387.3; 424/133.1, 424/185.1, 424/192.1, 424/193.1, 435/69.3, 530/350, 530/395
FIELD-OF-SEARCH: 530/350, 530/395, 530/403, 530/387.3, 435/69.3, 424/185.1, 424/193.1, 424/192.1, 424/133.1

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
5130297	July 1992	Sharma et al.	N/A
5194425	March 1993	Sharma et al.	N/A
5260422	November 1993	Clark et al.	N/A
5284935	February 1994	Clark et al.	N/A
5399567	March 1995	Platt et al.	N/A
5627048	May 1997	Afanasieo et al.	N/A
5656641	August 1997	Platt et al.	N/A
5801185	September 1998	Platt et al.	N/A
5820866	October 1998	Kappler et al.	N/A
5869270	February 1999	Rhode et al.	N/A
5976551	November 1999	Mottez et al.	N/A

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 89/12458	December 1989	WOX	
WO 92/18150	October 1992	WOX	
WO 93/10220	March 1993	WOX	
WO 93/09810	May 1993	WOX	
WO 94/18998	September 1994	WOX	
WO 94/25054	November 1994	WOX	
WO 95/23814	September 1995	WOX	
WO 96/04314	February 1996	WOX	
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WO 97/28191	August 1997	WOX	

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D. H. Margulies, et al., "Engineering Soluble Major Histocompatibility Molecules: Why and How", Immunol. Res., 6: pp. 101-116 (1987).
B. Nag, et al., "Stimulation of T cells by Antigenic Peptide Complexed With Isolated Chains of Major Histocompatibility Complex Class II Molecules", Proc. Natl. Acad. Sci. USA, 90: pp. 1604-1608 (1993).

ART-UNIT: 164
PRIMARY-EXAMINER: Saunders; David
ASSISTANT-EXAMINER: DeCloux; Amy
ATTY-AGENT-FIRM: Corless; Peter F. Buchanan; Robert L.

ABSTRACT:

The present invention relates to novel complexes of major histocompability complex (MHC) molecules and uses of such complexes. In one aspect, the invention relates to single chain MHC class II complexes that include a class II .beta.2 chain modification, e.g., deletion of essentially the entire class II .beta.2 chain. In another aspect, the invention features single chain MHC class II which comprise an immunoglobin constant chain or fragment. Further provided are polyspecific MHC complexes comprising at least one single chain MHC class II molecule. MHC complexes of the invention are useful for a variety of applications including: 1) in vitro screens for identification and isolation of peptides that modulate activity of selected T cells, including peptides that are T cell receptor antagonists and partial agonists, and 2) methods for suppressing or inducing an immune response in a mammal.

20 Claims, 32 Drawing figures

☐ 3. Document ID: US 6180377 B1

L6: Entry 3 of 28 File: USPT Jan 30, 2001

US-PAT-NO: 6180377
DOCUMENT-IDENTIFIER: US 6180377 B1

TITLE: Humanized antibodies

DATE-ISSUED: January 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Morgan; Susan Adrienne	Slough	N/A	N/A	GBX
Emtage; John Spencer	Marlow	N/A	N/A	GBX
Bodmer; Mark William	South Hinksey	N/A	N/A	GBX
Athwal; Diljeet Singh	London	N/A	N/A	GBX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Celltech Therapeutics Limited	N/A	N/A	N/A	GBX	03

APPL-NO: 8/ 569147
DATE FILED: March 25, 1996

PARENT-CASE:
REFERENCE TO RELATED APPLICATIONS This application is a national phase of International Application No. PCT/GB94/01291, filed Jun. 15, 1994, which claims priority to GB 9312415.4, filed Jun. 16, 1993, GB 9401597.1, filed Jan. 27, 1994, GB 9402499.9, filed Feb. 9, 1994 and GB 9406222.1, filed Mar. 29, 1994.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	9312415	June 16, 1993
GB	9401597	January 27, 1994
GB	9402499	February 9, 1994
GB	9406222	March 29, 1994

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/GB94/01291	June 15, 1993	WO94/29451	Dec 22, 1994	Mar 25, 1996	Mar 25, 1996

INT-CL: [7] C12N 15/00, C12N 1/20, C07H 21/04, C07K 16/00
US-CL-ISSUED: 435/172.3; 435/320.1, 435/252.3, 435/325, 530/387.1, 530/387.3, 530/388.1, 536/23.1
US-CL-CURRENT: 424/133.1; 435/252.3, 435/320.1, 435/325, 530/387.1, 530/387.3, 530/388.1, 536/23.1
FIELD-OF-SEARCH: 530/387.3, 530/172.3, 530/387.1, 530/388.1, 435/320.1, 435/252.3, 435/172.2, 435/325, 424/192.1, 424/141.1, 424/152.1, 536/23.1

PRIOR-ART-DISCLOSED:

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0068790 A1	January 1983	EPX	
0239400	March 1987	EPX	
0307434 B1	September 1993	EPX	
WO 90/07861	July 1990	WOX	
WO 91/09967	July 1991	WOX	
WO 91/09968	July 1991	WOX	
WO 92/01472	February 1992	WOX	
WO 92/11383	July 1992	WOX	

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ART-UNIT: 162
PRIMARY-EXAMINER: Ungar; Susan
ATTY-AGENT-FIRM: Woodcock Washburn Kurtz Mackiewicz & Norris LLP

ABSTRACT:

The invention describes humanized antibodies having specificity for the epitope recognised by the murine monoclonal antibody L243. Also described are processes for preparing said antibodies and pharmaceutical compositions and medical uses of said antibodies.

17 Claims, 21 Drawing figures

☐ 4. Document ID: US 6103239 A

L6: Entry 4 of 28 File: USPT Aug 15, 2000

US-PAT-NO: 6103239
DOCUMENT-IDENTIFIER: US 6103239 A

TITLE: Modified HGP-30 heteroconjugates, compositions and methods of use

DATE-ISSUED: August 15, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zimmerman; Daniel H.	Bethesda	MD	N/A	N/A
Sarin; Prem S.	Gaithersburg	MD	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
CEL-SCI Corporation	Vienna	VA	N/A	N/A	02

APPL-NO: 8/ 695304
DATE FILED: August 9, 1996

INT-CL: [7] A61K 39/21
US-CL-ISSUED: 424/188.1; 424/185.1, 424/196.11, 530/324, 530/327, 530/826, 519/12, 519/13
US-CL-CURRENT: 424/188.1; 424/185.1, 424/196.11, 514/12, 514/13, 530/324, 530/327, 530/826
FIELD-OF-SEARCH: 514/12, 514/13, 424/185.1, 424/186.1, 424/188.1, 424/196.11, 424/187.1, 530/324, 530/327, 530/826

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4983387	January 1991	Goldstein et al.	N/A

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0620010	October 1994	EPX	
89/12458	0000	WOX	
WO 89/12458	December 1989	WOX	

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ART-UNIT: 165
PRIMARY-EXAMINER: Stucker; Jeffrey
ATTY-AGENT-FIRM: Shelman & Shalloway

ABSTRACT:

A heteroconjugate is formed by linking a T cell binding ligand (TCBL) such as Peptide J of .beta.-2 microglobulin to a modified HGP-30 antigentic peptide

fragment of p17 gag peptide, such as. for example

ATL YSV HQR IDV KDT

KEA LEK IEE EQN KS (SEQ ID NO: 5)

The heteroconjugate is effective in eliciting a THI directed immune response and provides a vaccine composition for treating or preventing AIDS.

4 Claims, 0 Drawing figures

☐ 5. Document ID: US 6060309 A

L6: Entry 5 of 28 File: USPT May 9, 2000

US-PAT-NO: 6060309
DOCUMENT-IDENTIFIER: US 6060309 A

TITLE: Immune mediators and related methods

DATE-ISSUED: May 9, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kindsvogel; Wayne	Seattle	WA	N/A	N/A
Reich; Eva Pia	Palo Alto	CA	N/A	N/A
Gross; Jane A.	Seattle	WA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Anergen, Inc.	Redwood City	CA	N/A	N/A	02

APPL-NO: 8/ 855925
DATE FILED: May 14, 1997

PARENT-CASE:
This is a continuation of application Ser. No. 08/483,241, filed Jun. 7, 1995, now abandoned.

INT-CL: [7] C12N 5/06, C07K 16/28, C07K 17/14
US-CL-ISSUED: 435/325; 530/350, 530/387.1, 530/388.2, 530/388.22, 530/388.75, 530/389.6, 530/391.1
US-CL-CURRENT: 435/325; 530/350, 530/387.1, 530/388.2, 530/388.22, 530/388.75, 530/389.6, 530/391.1
FIELD-OF-SEARCH: 435/325, 530/387.1, 530/388.2, 530/388.22, 530/388.75, 530/389.6, 530/391.1, 530/350

PRIOR-ART-DISCLOSED:

OTHER PUBLICATIONS

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ART-UNIT: 164
PRIMARY-EXAMINER: Saunders; David
ASSISTANT-EXAMINER: VanderVegt; F. Pierre
ATTY-AGENT-FIRM: Townsend and Townsend and Crew LLP

ABSTRACT:

A method for preparing a responder cell clone that proliferates when combined with a selected antigenic peptide presented by a stimulator cell is disclosed. CD56 negative, CD8 negative responder cells are isolated from peripheral blood mononucleocytes and stimulated with pulsed or primed stimulator cells. Responder cell clones from prediabetic or new onset diabetic patients which are specific for GAD peptides are also disclosed.

4 Claims, 0 Drawing figures

☐ 6. Document ID: US 6022863 A

L6: Entry 6 of 28 File: USPT Feb 8, 2000

US-PAT-NO: 6022863
DOCUMENT-IDENTIFIER: US 6022863 A

TITLE: Regulation of gene expression

DATE-ISSUED: February 8, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Peyman; John A.	Cheshire	CT	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
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APPL-NO: 8/ 646789
DATE FILED: May 21, 1996

INT-CL: [6] C12N 15/11
US-CL-ISSUED: 514/44; 536/24.1, 435/325, 435/1.1, 435/91.1, 800/13, 800/25
US-CL-CURRENT: 514/44; 435/1.1, 435/325, 435/91.1, 536/24.1, 800/13, 800/25
FIELD-OF-SEARCH: 536/23.1, 536/24.1, 536/24.33, 435/325, 435/1.1, 435/91.1, 514/44, 800/13, 800/25

PRIOR-ART-DISCLOSED:

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FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
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ART-UNIT: 163
PRIMARY-EXAMINER: Martinell; James
ATTY-AGENT-FIRM: Pennie & Edmonds LLP

ABSTRACT:

The present invention relates to utrons, RNA molecules which contain promoter regulatory motif(s) and DNA analogs thereof and DNA molecules that can be transcribed to produce the foregoing. In particular, the invention provides gene promoter suppressing nucleic acids which suppress transcription from a

promoter of interest. In a preferred embodiment, the invention provides the TSU gene, nucleotide sequences of the TSU gene and RNA, as well as fragments, homologs and derivatives thereof. Methods of isolating TSU genes are also provided. Therapeutic and diagnostic methods and pharmaceutical compositions are also provided. In particular, the invention relates to methods for cell replacement therapy, gene therapy or organ transplantation wherein TSU nucleic acids suppress MHC class I and II gene expression, thus preventing immuno-rejection of non-autologous cells or organs. The invention also provides methods for treatment of diseases or disorders by suppression of MHC class I, MHC class II, ICAM-1, B7-1, B7-2, and/or Fc.gamma.R expression by provision of TSU function.

77 Claims, 43 Drawing figures

☐ 7. Document ID: US 6015884 A

L6: Entry 7 of 28 File: USPT Jan 18, 2000

US-PAT-NO: 6015884
DOCUMENT-IDENTIFIER: US 6015884 A

TITLE: Soluble divalent and multivalent heterodimeric analogs of proteins

DATE-ISSUED: January 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schneck; Jonathan	Silver Spring	MD	N/A	N/A
O'Herrin; Sean	Baltimore	MD	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The Johns Hopkins University	Baltimore	MD	N/A	N/A	02

APPL-NO: 8/ 828712
DATE FILED: March 28, 1997

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a continuation-in-part of Provisional Application Ser. No. 60/014,367, which was filed Mar. 28, 1996.

INT-CL: [6] C07K 16/00, C12P 21/08
US-CL-ISSUED: 530/387.3; 530/388.1
US-CL-CURRENT: 530/387.3; 530/388.1
FIELD-OF-SEARCH: 530/387.3, 530/388.1

PRIOR-ART-DISCLOSED:

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
93/10220	May 1993	WOX	
96/04314	February 1996	WOX	

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ART-UNIT: 162
PRIMARY-EXAMINER: Hutzell; Paula K.
ASSISTANT-EXAMINER: Bansal; Geetha P.
ATTY-AGENT-FIRM: Banner & Witcoff, Ltd.

ABSTRACT:

Specificity in immune responses is in part controlled by the selective interaction of T cell receptors with their cognate ligands, peptide/MHC molecules. The discriminating nature of this interaction makes these molecules, in soluble form, good candidates for selectively regulating immune responses. Attempts to exploit soluble analogs of these proteins has been hampered by the intrinsic low avidity of these molecules for their ligands. To increase the avidity of soluble analogs for their cognates to biologically relevant levels, divalent peptide/MHC complexes or T cell receptors (superdimers) were constructed. Using a recombinant DNA strategy, DNA encoding either the MHC class II/peptide or TCR heterodimers was ligated to DNA coding for murine Ig heavy and light chains. These constructs were subsequently expressed in a baculovirus expression system. Enzyme-linked immunosorbant assays (ELISA) specific for the Ig and polymorphic determinants of either the TCR or MHC fraction of the molecule indicated that infected insect cells secreted approximately 1 .mu.g/ml of soluble, conformationally intact chimeric superdimers. SDS PAGE gel analysis of purified protein showed that expected molecular weight species. The results of flow cytometry demonstrated that the TCR and class II chimeras bound specifically with high avidity to cells bearing their cognate receptors. These superdimers will be useful for studying TCR/MHC interactions, lymphocyte tracking, identifying new antigens, and have possible uses as specific regulators of immune responses.

10 Claims, 18 Drawing figures

☐ 8. Document ID: US 5969109 A

L6: Entry 8 of 28 File: USPT Oct 19, 1999

US-PAT-NO: 5969109
DOCUMENT-IDENTIFIER: US 5969109 A

TITLE: Chimeric antibodies comprising antigen binding sites and B and T cell epitopes

DATE-ISSUED: October 19, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bona; Constantin	New York	NY	10022	N/A
Zaghouani; Habib	Knoxville	TN	37919	N/A

APPL-NO: 8/ 363276
DATE FILED: December 22, 1994

PARENT-CASE:
SPECIFICATION This application is a continuation-in-part of U.S. Ser. No. 07/486,546, filed Feb. 28, 1990, now abandoned, of U.S. Ser. No. 07/687,376 filed on Apr. 18, 1991 now abandoned, and of U.S. Ser. No. 08/327,636 filed on Oct. 24, 1994, now abandoned, which are incorporated by reference herein.

INT-CL: [6] C07K 16/00, C12P 21/08
US-CL-ISSUED: 530/387.3; 530/387.1, 530/388.1, 530/388.2, 530/388.73, 530/388.75
US-CL-CURRENT: 530/387.3; 530/387.1, 530/388.1, 530/388.2, 530/388.73, 530/388.75
FIELD-OF-SEARCH: 530/387.3, 530/387.1, 530/388.1, 530/388.2, 530/388.73, 530/388.75

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
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5231167	July 1993	Zanetti et al.	N/A
5508386	April 1996	Zanetti et al.	530/387.3

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ART-UNIT: 162
PRIMARY-EXAMINER: Hutzell; Paula K.
ASSISTANT-EXAMINER: Ungar; Susan
ATTY-AGENT-FIRM: Kole; Lisa B.

ABSTRACT:

The present invention relates to chimeric antibodies which comprise a B cell epitope, a T cell epitope, and/or an antigen binding site. The chimeric antibodies may be produced by replacing at least a portion of an immunoglobulin molecule with the desired epitope or antigen binding site such that the functional capabilities of the epitope and the parent immunoglobulin are retained. The chimeric antibodies of the invention may be used to enhance an immune response against pathogens and tumor cells in subjects in need of such treatment.

6 Claims, 51 Drawing figures

☐ 9. Document ID: US 5908762 A

L6: Entry 9 of 28 File: USPT Jun 1, 1999

US-PAT-NO: 5908762
DOCUMENT-IDENTIFIER: US 5908762 A

TITLE: Transcription factor regulating MHC expression CDNA and genomic clones encoding same and retroviral expression constructs thereof

DATE-ISSUED: June 1, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ono; Santa Jeremy	Baltimore	MD	N/A	N/A
Strominger; Jack L.	Lexington	MA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The Johns Hopkins University	Cambridge	MA	N/A	N/A	02

APPL-NO: 8/ 828584
DATE FILED: March 31, 1997

PARENT-CASE:
This application is a division of application Ser. No. 08/327,832, filed Oct. 21, 1994.

INT-CL: [6] C12P 21/00, C12N 5/10, C12N 15/12, C07H 21/04
US-CL-ISSUED: 435/69.1; 435/367, 435/372, 435/372.3, 435/6, 536/23.5, 536/24.31

US-CL-CURRENT: 435/69.1; 435/367, 435/372, 435/372.3, 435/6, 536/23.5, 536/24.31
FIELD-OF-SEARCH: 536/23.5, 536/24.31, 435/6, 435/69.1, 435/325, 435/367, 435/372, 435/372.3

PRIOR-ART-DISCLOSED:

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4446128	May 1984	Baschang et al.	424/194.1
5166059	November 1992	Pastan et al.	435/69.7

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ART-UNIT: 185
PRIMARY-EXAMINER: Elliott; George C.
ASSISTANT-EXAMINER: Schwartzman; Robert
ATTY-AGENT-FIRM: Banner & Witcoff, Ltd.

ABSTRACT:

The present invention relates to NF-X1, a novel DNA binding protein which regulates expression of major histocompatibility complex (MHC) class II molecules, and to DNA sequences which encode the protein as well as recombinant expression of the protein. NF-X1 is a newly identified, cysteine-rich polypeptide which interacts sequence-specifically with the conserved X1 box regulatory element found in the proximal promoters of class II MHC genes. A cysteine-rich domain within NF-X1 contains a motif repeated seven times, and this entire region is necessary and sufficient for both sequence specific binding and effector function. The motif is related to but distinct from the previously described metal-binding protein families: LIM domain and RING finger. NFX.1 mRNA is markedly overexpressed late after induction of cells with interferon-gamma, and this overexpression coincides with a reduction in the level of HLA-DRA transcript in these cells. Overexpression of this protein strongly and specifically represses the transcription of the HLA-DRA gene in MHC class II positive cell lines, indicating that the NF-X1 protein is a transcriptional repressor of MHC class II molecules.

11 Claims, 26 Drawing figures

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L6: Entry 10 of 28 File: USPT May 25, 1999

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DOCUMENT-IDENTIFIER: US 5906928 A

TITLE: Efficient gene transfer into primary murine lymphocytes obviating the need for drug selection

DATE-ISSUED: May 25, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dougherty; Joseph	Hampton	NJ	N/A	N/A
Ron; Yacov	East Brunswick	NJ	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
University of Medicine and Dentistry of New Jersey	Newark	NJ	N/A	N/A	02

APPL-NO: 8/ 586754
DATE FILED: March 19, 1996

PARENT-CASE:
This application is a 371 application of PCT/US94/08612, filed Aug. 1, 1994 and is a continuation-in-part of Ser. No. 08/100,546, filed Jul. 30, 1993, now abandoned.

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APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
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US-CL-ISSUED: 435/172.3; 435/320.1, 435/355, 435/357, 435/372, 435/372.2, 435/372.3, 435/373
US-CL-CURRENT: 435/457; 435/320.1, 435/355, 435/357, 435/372, 435/372.2, 435/372.3, 435/373
FIELD-OF-SEARCH: 435/5, 435/6, 435/172.3, 435/320.1, 435/240.2, 435/355, 435/357, 435/372, 435/373, 435/372.2, 435/372.3, 435/366, 435/354, 435/235.1

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PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
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4980289	December 1990	Temin et al.	435/235.1
5124263	June 1992	Temin et al.	435/240.2
5399346	March 1995	Anderson et al.	424/93.21

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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 89/11539	November 1989	WOX	
WO 93/07281	April 1993	WOX	

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ART-UNIT: 185
PRIMARY-EXAMINER: Guzo; David
ATTY-AGENT-FIRM: Klauber & Jackson

ABSTRACT:

The present invention pertains to a method for efficiently introducing exogenous genes into primary lymphoid cells without drug selection which comprises the steps (a) deriving a retroviral vector and a helper cell combination that will yield a level of virus production in the range from 5.times.10.sup.6 to 5.times.10.sup.7 units/ml by transfecting a vector into a helper cell followed by selection, isolation of cell clones, and determination of viral titers to identify which virus-producing cell lines produce a virus

titer in the range from 5.times.10.sup.6 to 5.times.10.sup.7 units/ml; (b) isolating a lymphoid cell subpopulation which can repopulate a specific lymphoid lineage or is a long-lived population by treating a suspension of lymphoid cells with a monoclonal antibody which removes undesired lymphoid cells to obtain an enriched lymphoid subpopulation; (c) culturing the enriched lymphoid subpopulation from step (b) with growth factors specific to the lymphoid subpopulation; (d) co-cultivating the lymphoid subpopulation from step (c) with a lawn of irradiated virus-producing cell line from step (a) to produce an infected lymphoid subpopulation; and (e) harvesting the infected lymphoid subpopulation. The invention further relates to a population of transfected lymphocytes, in which greater than about 90% of the lymphocytes contain a provirus.

30 Claims, 18 Drawing figures

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DOCUMENT-IDENTIFIER: US 5876708 A

TITLE: Allogeneic and xenogeneic transplantation

DATE-ISSUED: March 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sachs; David H.	Newton	MA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The General Hospital Corporation	Boston	MA	N/A	N/A	02

APPL-NO: 8/ 458720
DATE FILED: June 1, 1995

PARENT-CASE:
This application is a continuation-in-part of Ser. No. 08/266,427, filed Jun. 27, 1994, now issued as U.S. Pat. No. 5,614,187; and a continuation-in-part of Ser. No. 08/451,210, filed May 26, 1995, now pending which is a file wrapper continuation of Ser. No. 07/838,595, filed May 26, 1995, now abandoned; and a continuation-in-part of Ser. No. 08/220,371, filed Mar. 29, 1994, now abandoned; and a continuation-in-part of PCT/US94/05527, filed May 16, 1994, now completed; and a continuation-in-part of Ser. No. 08/243,653, filed May 16, 1994, now issued as U.S. Pat. No. 5,685,564; and a continuation-in-part of Ser. No. 08/114,072, filed Aug. 30, 1993, now issued as U.S. Pat. No. 5,624,823; and a continuation-in-part of Ser. No. 08/150,739, filed Nov. 10, 1993, now abandoned; and a continuation-in-part of Ser. No. 08/212,228, filed Mar. 14, 1994, now abandoned; and a continuation-in-part of PCT/US94/01616 filed Feb. 14, 1994, now completed.

INT-CL: [6] A61K 38/00, C12N 5/08
US-CL-ISSUED: 424/93.1; 435/325
US-CL-CURRENT: 424/93.1; 435/325
FIELD-OF-SEARCH: 424/93.1, 424/93.21, 435/32.5

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U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
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5597563	January 1997	Beschorner	424/93.7

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Thomas et al. Ann. Surg. 198(3): 370, 1983.
Kahin NEJM 321(25): 1725, 1989.

ART-UNIT: 162
PRIMARY-EXAMINER: Chambers; Jasemine C.
ASSISTANT-EXAMINER: Hauda; Karen M.
ATTY-AGENT-FIRM: Myers, Esq.; Louis

ABSTRACT:

Methods of inducing tolerance including administering to the recipient a short course of help reducing treatment or administering a short course and methods of prolonging the acceptance of a graft by administering a short course of an immunosuppressant.

79 Claims, 14 Drawing figures

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Drawi Desc | Image

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☐ 12. Document ID: US 5869270 A

L6: Entry 12 of 28 File: USPT Feb 9, 1999

US-PAT-NO: 5869270
DOCUMENT-IDENTIFIER: US 5869270 A

TITLE: Single chain MHC complexes and uses thereof

DATE-ISSUED: February 9, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rhode; Peter R.	Miami	FL	N/A	N/A
Jiao; Jin-An	Fort Lauderdale	FL	N/A	N/A
Burkhardt; Martin	Miami	FL	N/A	N/A
Wong; Hing C.	Fort Lauderdale	FL	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Sunol Molecular Corporation	Miami	FL	N/A	N/A	02

APPL-NO: 8/ 596387
DATE FILED: January 31, 1996

INT-CL: [6] G01N 33/53
US-CL-ISSUED: 435/7.24; 435/69.7, 435/320.1, 435/325, 435/252.3, 530/350, 536/23.5, 536/24.1
US-CL-CURRENT: 435/7.24; 435/252.3, 435/320.1, 435/325, 435/69.7, 530/350, 536/23.5, 536/24.1
FIELD-OF-SEARCH: 530/350, 530/387.1, 536/23.4, 536/24.1, 435/69.7, 435/252.3, 435/320.1, 435/325, 435/7.24

PRIOR-ART-DISCLOSED:

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PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
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5194425	March 1993	Sharma et al.	424/193.1
5260422	November 1993	Clark et al.	424/185.1
5284935	February 1994	Clark et al.	424/185.1

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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
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WO 92/18150	October 1992	WOX	
WO 93/10220	March 1993	WOX	
WO 93/09810	May 1993	WOX	
WO 94/18998	September 1994	WOX	
WO 94/25054	November 1994	WOX	
WO 95/23814	September 1995	WOX	

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ART-UNIT: 166
PRIMARY-EXAMINER: Walsh; Stephen
ASSISTANT-EXAMINER: Brown; Karen E.
ATTY-AGENT-FIRM: Corless; Peter F. Buchanan; Robert L. Dike, Bronstein, Roberts & Cushman, LLP

ABSTRACT:

The present invention relates to novel complexes of major histocompatibility complex (MHC) molecules and uses of such complexes. In one aspect, the invention relates to loaded MHC complexes that include at least one MHC molecule with a peptide-binding groove and a presenting peptide non-covalently linked to the MHC protein. In another aspect, the invention features single chain MHC class II peptide fusion complexes with a presenting peptide covalently linked to the peptide binding grove of the complex. MHC complexes of the invention are useful for a variety of applications including: 1) in vitro screens for identification and isolation of peptides that modulate activity of selected T cells, including peptides that are T cell receptor antagonists and partial agonists, and 2) methods for suppressing or inducing an immune response in a mammal.

38 Claims, 82 Drawing figures

☐ 13. Document ID: US 5866760 A

L6: Entry 13 of 28 File: USPT Feb 2, 1999

US-PAT-NO: 5866760
DOCUMENT-IDENTIFIER: US 5866760 A

TITLE: Stat6 deficient transgenic mice

DATE-ISSUED: February 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Grusby; Michael J.	Boston	MA	N/A	N/A
Kaplan; Mark H.	Boston	MA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
President and Fellows of Harvard College	Cambridge	MA	N/A	N/A	02

APPL-NO: 8/ 823051
DATE FILED: March 21, 1997

INT-CL: [6] C12N 5/00, C12N 15/00, C12N 15/09
US-CL-ISSUED: 800/18; 435/455, 435/462, 435/463, 435/325, 435/320.1, 435/92.1, 424/9.21
US-CL-CURRENT: 800/18; 424/9.2, 435/320.1, 435/325, 435/455, 435/462, 435/463, 800/3
FIELD-OF-SEARCH: 800/2, 800/18, 435/172.3, 435/69.1, 435/325, 435/320.1, 435/92.1, 435/455, 435/462, 435/463, 424/9.21

PRIOR-ART-DISCLOSED:

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Copies of pages from lab notebook (4p).
Keystone symposium agenda (6p).
St. Jude Children's Research Hospital interoffice memorandum (2p).

ART-UNIT: 162
PRIMARY-EXAMINER: Chambers; Jasemine C.
ASSISTANT-EXAMINER: Martin; Jill D.
ATTY-AGENT-FIRM: Osman; Richard Aron

ABSTRACT:

The invention provides methods and compositions for evaluating modulators of the Stat6 signaling pathway; in a particular, transgenic mice comprising a transgene within a Stat6 allele locus, encoding a selectable marker and displacing the SH2-encoding domain of the Stat6 allele. More particularly, the transgene may comprise 3' and 5' regions with sufficient complementarity to the natural Stat6 allele at the locus to effect homologous recombination of the transgene with the Stat6 allele. Such mice provide useful animal models for determining the effect of candidate drugs on a host deficient in Stat6 function. The invention provides a variety of methods for making and using the subject compositions; in particular, methods for determining the effect of a candidate drug on a mouse deficient in Stat6 function and methods of evaluating the side effects of a Stat6 function inhibitor.

2 Claims, 1 Drawing figures

☐ 14. Document ID: US 5859226 A

L6: Entry 14 of 28 File: USPT Jan 12, 1999

US-PAT-NO: 5859226
DOCUMENT-IDENTIFIER: US 5859226 A

TITLE: Polynucleotide decoys that inhibit MHC-II expression and uses thereof

DATE-ISSUED: January 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hunt; C. Anthony	San Francisco	CA	N/A	N/A
Lim; Carol	San Francisco	CA	N/A	N/A
Garovoy; Marvin R.	San Anselmo	CA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Regents of the University of California, The	Oakland	CA	N/A	N/A	02

APPL-NO: 8/ 281423
DATE FILED: July 27, 1994

PARENT-CASE:
CROSS-REFERENCE TO A RELATED APPLICATION This application is a continuation-in-part of U.S. patent application Ser. No. 08/100,088, filed Jul. 29, 1993, now abandoned the disclosure of which is incorporated herein by reference.

INT-CL: [6] C07H 21/04
US-CL-ISSUED: 536/24.1; 514/44, 514/6, 514/172.3, 514/325, 514/91.1, 514/1.2
US-CL-CURRENT: 536/24.1; 435/325, 435/6, 435/91.1, 435/91.2
FIELD-OF-SEARCH: 514/44, 435/6, 435/91.1, 435/91.2, 435/172.3, 435/325, 536/23.1, 536/24.1, 935/33, 935/34

PRIOR-ART-DISCLOSED:

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
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WO 90/12812	November 1990	WOX	
WO 92/18522	October 1992	WOX	
WO 92/19732	November 1992	WOX	
WO 93/02188	February 1993	WOX	
WO 93/14768	August 1993	WOX	

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ART-UNIT: 184
PRIMARY-EXAMINER: Low; Christopher S.F.
ASSISTANT-EXAMINER: Nguyen; Dave Trong
ATTY-AGENT-FIRM: Morrison & Foerster LLP

ABSTRACT:

The invention is directed to a newly discovered class of polynucleotide decoys that is capable of competitively inhibiting the binding of transcription factors to the X-box sequence. This binding is necessary for the expression of MHC-II genes. The invention is also directed to methods of preparing these polynucleotide decoys, and methods of use thereof. In particular, we have identified a class of polynucleotide decoys that mimic the X-Box of MHC-II and competitively bind the MHC-II transcription factor RF-X, resulting in the modulation of MHC-II antigen expression. Thus, the invention can be used to inhibit the expression of HLA molecules on the surface of donor cells or organs, in order to render them invisible to the host's immune system, or in methods of treating an individual with an autoimmune disease characterized by dysfunctional expression of an MHC class II antigen. Further, because of the role of RF-X in the expression of several viral proteins, the polynucleotide decoys of the invention can be used in methods of treating an individual infected with hepatitis B virus, or cytomegalovirus.

2 Claims, 9 Drawing figures

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

☐ 15. Document ID: US 5840832 A

L6: Entry 15 of 28 File: USPT Nov 24, 1998

US-PAT-NO: 5840832
DOCUMENT-IDENTIFIER: US 5840832 A

TITLE: Transcription factor regulating MHC expression, CDNA and genomic clones encoding same and retroviral expression constructs thereof

DATE-ISSUED: November 24, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ono; Santa Jeremy	Baltimore	MD	N/A	N/A
Strominger; Jack L.	Lexington	MA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The Johns Hopkins University	Baltimore	MD	N/A	N/A	02
The President and Fellows of Harvard College	Cambridge	MA	N/A	N/A	02

APPL-NO: 8/ 327832
DATE FILED: October 21, 1994

INT-CL: [6] C07K 14/00, C07K 14/435, C12N 15/63
US-CL-ISSUED: 530/300; 530/350, 435/320.1
US-CL-CURRENT: 530/300; 435/320.1, 530/350
FIELD-OF-SEARCH: 530/350, 530/300, 435/320.1

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4399216	August 1983	Axel et al.	435/6
4446128	May 1984	Baschang et al.	424/88
5166059	November 1992	Pastan et al.	435/69.7

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Ono, et al., "Transcription of a subset of human class II major histocompatibility complex genes is regulated by a nucleoprotein complex that contains c-fos or an antigenically related protein," Proc. Natl. Acad. Sci. USA, 88:4304-4308 (1991).
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MP SRCH result 1, Accession No. P15472.
MP SRCH Result 2, Accession No. P14729.

ART-UNIT: 183
PRIMARY-EXAMINER: Elliott; George C.
ASSISTANT-EXAMINER: Wai; Thanda
ATTY-AGENT-FIRM: Banner & Witcoff, Ltd.

ABSTRACT:

The present invention relates to NF-X1, a novel DNA binding protein which regulates expression of major histocompatibility complex (MHC) class II molecules, and to DNA sequences which encode the protein as well as recombinant expression of the protein. NF-X1 is a newly identified, cysteine-rich polypeptide which interacts sequence-specifically with the conserved X1 box regulatory element found in the proximal promoters of class II MHC genes. A cysteine-rich domain within NF-X1 contains a motif repeated seven times, and this entire region is necessary and sufficient for both sequence specific binding and effector function. The motif is related to but distinct from the previously described metal-binding protein families: LIM domain and RING finger. NFX.1 mRNA is markedly overexpressed late after induction of cells with interferon-gamma, and this overexpression coincides with a reduction in the level of HLA-DRA transcript in these cells. Overexpression of this protein strongly and specifically represses the transcription of the HLA-DRA gene in MHC class II positive cell lines, indicating that the NF-X1 protein is a transcriptional repressor of MHC class II molecules.

5 Claims, 25 Drawing figures

☐ 16. Document ID: US 5824315 A

L6: Entry 16 of 28 File: USPT Oct 20, 1998

US-PAT-NO: 5824315
DOCUMENT-IDENTIFIER: US 5824315 A

TITLE: Binding affinity of antigenic peptides for MHC molecules

DATE-ISSUED: October 20, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nag; Bishwajit	Fremont	CA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Anergen, Inc.	Redwood City	CA	N/A	N/A	02

APPL-NO: 8/ 640344
DATE FILED: April 30, 1996

PARENT-CASE:
This is a continuation-in-part of co-pending U.S. patent application Ser. No. 08/227,371, filed Apr. 14, 1994, pending. This application also is a continuation-in-part of co-pending U.S. patent application Ser. No. 08/329,010, filed Oct. 25, 1994, pending, which is a continuation-in-part of U.S. patent application Ser. No. 08/143,575 filed Oct. 25, 1993, now abandoned. All of the above applications are hereby incorporated by reference in their entirety.

INT-CL: [6] A61K 39/00
US-CL-ISSUED: 424/195.11; 424/185.1, 424/193.1
US-CL-CURRENT: 424/195.11; 424/185.1, 424/193.1
FIELD-OF-SEARCH: 424/193.1, 424/195.11, 424/185.1

PRIOR-ART-DISCLOSED:

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PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
5130297	July 1992	Sharma et al.	N/A
5194425	March 1993	Sharma et al.	N/A
5260422	November 1993	Clark et al.	N/A
5399347	March 1995	Trentham et al.	N/A
5468481	November 1995	Sharma et al.	N/A
5595881	January 1997	Kendricks	N/A

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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 91/18012	November 1992	WOX	
WO 94/03205	February 1994	WOX	

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ART-UNIT: 186
PRIMARY-EXAMINER: Cunningham; Thomas M.
ASSISTANT-EXAMINER: Lubet; Martha
ATTY-AGENT-FIRM: Townsend and Townsend and Crew, LLP

ABSTRACT:

This invention provides methods of improving the binding affinity of a peptide epitope for MHC Class II molecules by attaching to the N-terminus of the peptide epitope a hydrophobic amino acid or a peptide containing a hydrophobic amino acid. The invention also provides complexes between the modified

antigenic peptides and MHC Class II molecules, as well as method for treating deleterious immune responses.

32 Claims, 7 Drawing figures

☐ 17. Document ID: US 5756096 A

L6: Entry 17 of 28 File: USPT May 26, 1998

US-PAT-NO: 5756096
DOCUMENT-IDENTIFIER: US 5756096 A

TITLE: Recombinant antibodies for human therapy

DATE-ISSUED: May 26, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Newman; Roland A.	San Diego	CA	N/A	N/A
Hanna; Nabil	Olivenhain	CA	N/A	N/A
Raab; Ronald W.	San Diego	CA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
IDEC Pharmaceuticals Corporation	San Diego	CA	N/A	N/A	02

APPL-NO: 8/ 476237
DATE FILED: June 7, 1995

PARENT-CASE:
FIELD OF THE INVENTION This application is a continuation-in-part of U.S. Ser. No. 08/379,072, filed Jan. 25, 1995 (U.S. Pat. No. 5,658,570), which is a continuation of U.S. Ser. No. 07/912,292 (abandoned), filed Jul. 10, 1992, which is a continuation-in-part of Newman et al., U.S. patent application Ser. No. 07/856,281, filed Mar. 23, 1992 (abandoned), which is a continuation-in-part of U.S. patent application Ser. No. 07/735,064, filed Jul. 25, 1991 (abandoned), the whole of which, including drawings, are hereby incorporated by reference. This invention relates to recombinant antibodies useful for human therapy, and to methods for production of such antibodies.

INT-CL: [6] A61K 39/395
US-CL-ISSUED: 424/154.1; 424/133.1, 424/141.1, 530/387.1
US-CL-CURRENT: 424/154.1; 424/133.1, 424/141.1, 530/387.1
FIELD-OF-SEARCH: 424/133.1, 424/141.1, 424/154.1, 530/387.1

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4816397	March 1989	Boss et al.	435/69.1
4816567	March 1989	Cabilly et al.	530/387.1
4973745	November 1990	Schoemaker et al.	530/387.1
4975369	December 1990	Beavers et al.	435/69.1

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0451216 B1	October 1991	EPX	
523949A1	January 1993	EPX	
0682040 A1	November 1995	EPX	
9008198	July 1990	WOX	

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Truneh, A. et al., Cell Immun., 131:98 (1990).
Camerini, D. and Seed, B., Abstract No. T.C.P. 125, V International Conference on AIDS, p. 587 (1989).
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ART-UNIT: 186
PRIMARY-EXAMINER: Feisee; Lila
ASSISTANT-EXAMINER: Bansal; Geetha P.
ATTY-AGENT-FIRM: Burns, Doane, Swecker & Mathis, L.L.P.

ABSTRACT:

Chimeric antibodies including an Old World monkey portion and a human portion, nucleic acid encoding such antibodies, Old World monkey monoclonal antibodies, and methods for their production and use.

6 Claims, 26 Drawing figures

☐ 18. Document ID: US 5698679 A

L6: Entry 18 of 28 File: USPT Dec 16, 1997

US-PAT-NO: 5698679
DOCUMENT-IDENTIFIER: US 5698679 A

TITLE: Product and process for targeting an immune response

DATE-ISSUED: December 16, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nemazee; David A.	Denver	CO	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
National Jewish Center for Immunology and Respiratory Medicine	Denver	CO	N/A	N/A	02

APPL-NO: 8/ 309006
DATE FILED: September 19, 1994

INT-CL: [6] C12P 21/08, A61K 39/395, A61K 39/40, A61K 39/42
US-CL-ISSUED: 530/387.3; 424/130.1, 424/133.1, 424/134.1
US-CL-CURRENT: 530/387.3; 424/130.1, 424/133.1, 424/134.1
FIELD-OF-SEARCH: 530/387.3, 424/130.1

PRIOR-ART-DISCLOSED:

OTHER PUBLICATIONS

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ART-UNIT: 186
PRIMARY-EXAMINER: Feisee; Lila
ASSISTANT-EXAMINER: Eyler; Yvonne
ATTY-AGENT-FIRM: Sheridan Ross P.C.

ABSTRACT:

The present invention relates to a product and process for regulating an immune system using an immunoglobulin fusion protein capable of targeting a specific peptide precursor to a specific antigen presenting cell. Disclosed is a peptide precursor associated with an immunoglobulin molecule capable of binding to an antigen on the surface of an antigen presenting cell. Also disclosed is a nucleic acid molecule having a sequence encoding an immunoglobulin fusion protein comprising a peptide precursor and an immunoglobulin molecule. The invention is additionally directed to therapeutic reagents which can act as toleragens or immunogens useful in the regulation of an immune response.

27 Claims, 5 Drawing figures

☐ 19. Document ID: US 5670324 A

L6: Entry 19 of 28 File: USPT Sep 23, 1997

US-PAT-NO: 5670324
DOCUMENT-IDENTIFIER: US 5670324 A

TITLE: Use of chimeric CD4-src protein tyrosine kinases in drug screening and detection of an immune response

DATE-ISSUED: September 23, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Littman; Dan	San Francisco	CA	N/A	N/A
Xu; Hua	San Francisco	CA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The Regents of the University of California	Oakland	CA	N/A	N/A	02

APPL-NO: 8/ 459964
DATE FILED: June 2, 1995

PARENT-CASE:
This is a Division of application Ser. No. 08/112,912 filed Aug. 27, 1993, U.S. Pat. No. 5,439,819.

INT-CL: [6] C12Q 1/68
US-CL-ISSUED: 435/6; 435/15, 435/69.7
US-CL-CURRENT: 435/6; 435/15, 435/69.7
FIELD-OF-SEARCH: 435/6, 435/15, 435/69.7

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4929604	May 1990	Munford et al.	514/53

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Feig, Science 260, 767-768 (1993).

ART-UNIT: 187
PRIMARY-EXAMINER: Horlick; Kenneth R.
ATTY-AGENT-FIRM: Townsend and Townsend and Crew LLP

ABSTRACT:

The present invention provides chimeric proteins containing extracellular and transmembrane domains of CD4 and protein tyrosine kinases of the src family. Also provided are DNA molecules encoding the proteins of the present invention and cells containing such DNA molecules. The proteins and cells of the present invention may be employed in methods for identifying drugs that block T cell activation and for identifying low level self-antigens.

10 Claims, 15 Drawing figures

☐ 20. Document ID: US 5667998 A

L6: Entry 20 of 28 File: USPT Sep 16, 1997

US-PAT-NO: 5667998
DOCUMENT-IDENTIFIER: US 5667998 A

TITLE: Efficient gene transfer into primary lymphocytes obviating the need for drug selection

DATE-ISSUED: September 16, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dougherty; Joseph	Hampton	NJ	N/A	N/A
Kuo; Ming-Ling	Taipei	N/A	N/A	TWX
Sutkowski; Natalie	Gloucester	MA	N/A	N/A
Ron; Yacov	East Brunswick	NJ	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
University of Medicine and Dentistry of New Jersey	Newark	NJ	N/A	N/A	02

APPL-NO: 8/ 477363
DATE FILED: June 7, 1995

PARENT-CASE:
The present application is a continuation of copending International Application No. PCT/US94/08612, filed Aug. 1, 1994, which is a continuation-in-part of application Ser. No. 08/100,546, filed 30 Jul. 1993, now abandoned, and claims the benefit of the filing dates of the applications pursuant to 35 U.S.C. .sctn..sctn.120 and 365.

INT-CL: [6] C12N 5/10, C12N 15/64
US-CL-ISSUED: 435/172.3; 435/320.1, 435/355, 435/325
US-CL-CURRENT: 435/456; 435/320.1, 435/325, 435/355
FIELD-OF-SEARCH: 435/172.1, 435/172.3, 435/240.2, 435/5, 435/6, 435/320.1

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4650764	March 1987	Temin et al.	435/240.2
4980289	December 1990	Temin et al.	435/235.1
5124263	June 1992	Temin et al.	435/240.2
5399346	March 1995	Anderson et al.	424/93.21

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
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WO93/07281	April 1993	WOX	

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Mann et al., 1983, Cell 33: 153-59.

ART-UNIT: 185
PRIMARY-EXAMINER: Guzo; David
ATTY-AGENT-FIRM: Klauber & Jackson

ABSTRACT:

The present invention pertains to a method for efficiently introducing exogenous genes into primary lymphoid cells without drug selection which comprises the steps (a) deriving a retroviral vector and a helper cell combination that will yield a level of virus production in the range from 5.times.10.sup.6 to 5.times.10.sup.7 units/ml by transfecting a vector into a helper cell followed by selection, isolation of cell clones, and determination of viral titers to identify which virus-producing cell lines produce a virus titer in the range from 5.times.10.sup.6 to 5.times.10.sup.7 units/ml; (b) isolating a lymphoid cell subpopulation which can repopulate a specific lymphoid lineage or is a long-lived population by treating a suspension of lymphoid cells with a monoclonal antibody which removes undesired lymphoid cells to obtain an enriched lymphoid subpopulation; (c) culturing the enriched lymphoid subpopulation from step (b) with growth factors specific to the lymphoid subpopulation; (d) co-cultivating the lymphoid subpopulation from step (c) with a lawn of irradiated virus-producing cell line from step (a) to produce an infected lymphoid subpopulation; and (e) harvesting the infected lymphoid subpopulation. The invention further relates to a population of transfected lymphocytes, in which greater than about 90% of the lymphocytes contain a provirus.

13 Claims, 18 Drawing figures

☐ 21. Document ID: US 5644065 A

L6: Entry 21 of 28 File: USPT Jul 1, 1997

US-PAT-NO: 5644065
DOCUMENT-IDENTIFIER: US 5644065 A

TITLE: Genetically engineered mice containing alterations in the MHC class II genes

DATE-ISSUED: July 1, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Benoist; Christophe	Erstein	N/A	N/A	FRX
Mathis; Diane	Erstein	N/A	N/A	FRX
Cosgrove; Dominic	Omaha	NE	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Bristol-Myers Squibb Company	Princeton	NJ	N/A	N/A	02
Institut National de la Sante et de la Recherche Medicale	Paris Cedex	N/A	N/A	FRX	07
Centre National de la Recherche Scientifique	Paris Cedex	N/A	N/A	FRX	07
Universite Louis Pasteur	Strasbourg Cedex	N/A	N/A	FRX	03

APPL-NO: 8/ 312984
DATE FILED: October 3, 1994

PARENT-CASE:
This application is a continuation of application Ser. No. 07/819,497, filed Jan. 10, 1992 now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	9100481	January 10, 1991

INT-CL: [6] C12N 15/00
US-CL-ISSUED: 800/2; 435/172.3
US-CL-CURRENT: 800/11
FIELD-OF-SEARCH: 800/2

PRIOR-ART-DISCLOSED:

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ART-UNIT: 184
PRIMARY-EXAMINER: Ziska; Suzanne E.
ATTY-AGENT-FIRM: Sterne, Kessler, Goldstein & Fox, P.L.L.C.

ABSTRACT:

The present invention provides mice which are deficient in the normal expression of one or more MHC class II genes, to mice heterozygous for such deficiency, and to cell lines, preferably pluripotent or totipotent cell lines, which are heterozygous, homozygous or chimeric for such deficiency, as well as to the use of any of the above, especially in situations where the absence of at least one MHC gene, or the normal expression thereof, is desirable.

4 Claims, 12 Drawing figures

☐ 22. Document ID: US 5633234 A

L6: Entry 22 of 28 File: USPT May 27, 1997

US-PAT-NO: 5633234
DOCUMENT-IDENTIFIER: US 5633234 A

TITLE: Lysosomal targeting of immunogens

DATE-ISSUED: May 27, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
August; J. Thomas	Baltimore	MD	N/A	N/A
Pardoll; Drew M.	Baltimore	MD	N/A	N/A
Guarnieri; Frank G.	Baltimore	MD	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The Johns Hopkins University	Baltimore	MD	N/A	N/A	02

APPL-NO: 8/ 006845
DATE FILED: January 22, 1993

INT-CL: [6] A61K 31/70, C12N 15/62
US-CL-ISSUED: 514/44; 424/185.1, 424/192.1, 435/69.3, 435/252.3, 435/320.1, 530/350, 530/395, 530/806, 536/23.4, 536/23.5
US-CL-CURRENT: 514/44; 424/185.1, 424/192.1, 435/252.3, 435/320.1, 435/69.3, 530/350, 530/395, 530/806, 536/23.4, 536/23.5
FIELD-OF-SEARCH: 424/18, 424/185.1, 424/288.1, 435/69.3

PRIOR-ART-DISCLOSED:

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PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4400376	August 1983	Sanderson	N/A
4406885	September 1983	Pinter	N/A
4446128	May 1984	Baschang et al.	N/A
4448765	May 1984	Ash et al.	N/A
4454116	June 1984	Brinton	N/A
4578458	March 1986	Pier	N/A
4593002	June 1986	Dulbecco	N/A
4681762	July 1987	Oeschger et al.	N/A
4738846	April 1988	Rose et al.	N/A
4769330	September 1988	Paoletti	N/A
4920209	April 1990	Davis et al.	N/A

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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
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WO 93/06216	April 1993	WOX	

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Peters, et al., (1990) "Targeting of a Lysosomal Membrane Protein: a Tyrosine-Containing Endocytosis Signal in the Cytoplasmic Tail of Lysosomal Acid Phosphatase is Necessary and Sufficient for Targeting to Lysosomes", EMBO J., 9:3497-3506.
Williams, et al., (1990) "Accumulation of Membrane Glycoproteins in Lysosomes Requires a Tyrosine Residue at a Particular Position in the Cytoplasmic Tail", J. Cell. Biol., 111:955-966.
Mane, et al., (1989) "Purification and Characterization of Human Lysosomal Membrane Glycoproteins", Archiv. Biochem. Biophys., 268:360-378.
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ART-UNIT: 186
PRIMARY-EXAMINER: Cunningham; Thomas M.
ATTY-AGENT-FIRM: Banner & Witcoff, Ltd.

ABSTRACT:

The inventors have discovered a targeting signal that will direct proteins to the endosomal/lysosomal compartment, and they have demonstrated that chimeric proteins containing a luminal antigenic domain and a cytoplasmic endosomal/lysosomal targeting signal will effectively target antigens to that compartment, where the antigenic domain is processed and peptides from it are presented on the cell surface in association with major histocompatibility (MHC) class II molecules. Chimeric DNA encoding the antigen of interest, linked to an endosomal/lysosomal targeting sequence, inserted in an immunization vector, can introduce the chimeric genes into cells, where the recombinant antigens are expressed and targeted to the endosomal/lysosomal compartment. As a result, the antigens associate more efficiently with MHC class II molecules, providing enhanced in vivo stimulation of CD4.sup.+ T cells specific for the recombinant antigen. Delivering antigens to an endosomal/lysosomal compartment by means of chimeric constructs containing such lysosomal targeting signals will be of value in any vaccination or immunization strategy that seeks to stimulate CD4.sup.+ MHC class II restricted immune responses.

20 Claims, 19 Drawing figures

☐ 23. Document ID: US 5587455 A

L6: Entry 23 of 28 File: USPT Dec 24, 1996

US-PAT-NO: 5587455
DOCUMENT-IDENTIFIER: US 5587455 A

TITLE: Cytotoxic agent against specific virus infection

DATE-ISSUED: December 24, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Berger; Edward A.	Rockville	MD	N/A	N/A
Moss; Bernard	Bethesda	MD	N/A	N/A
Fuerst; Thomas R.	Gaithersburg	MD	N/A	N/A
Pastan; Ira	Potomac	MD	N/A	N/A
Fitzgerald; David	Rockville	MD	N/A	N/A
Mizukami; Tamio	Machida	N/A	N/A	JPX
Chaudhary; Vijay K.	New Delhi	N/A	N/A	INX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The United States of America as represented by the Department of Health and Human Services	Washington	DC			06

APPL-NO: 8/ 335669
DATE FILED: November 8, 1994

PARENT-CASE:
This is a continuation of application Ser. No. 08/022,182, filed on Feb. 25, 1993, abandoned, which is a divisional of U.S. Ser. No. 07/223,270, filed Jul. 22, 1988, now U.S. Pat. No. 5,206,353.

INT-CL: [6] C07K 14/21, C07K 14/73
US-CL-ISSUED: 530/324; 530/350
US-CL-CURRENT: 530/324; 530/350
FIELD-OF-SEARCH: 435/6, 435/7.2, 435/69.1, 435/69.7, 530/350, 530/324

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4545985	October 1985	Pastan et al.	424/180.1
4892827	January 1990	Pastan et al.	435/193

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO8903222	April 1989	WOX	
WO9004414	May 1990	WOX	

OTHER PUBLICATIONS

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Berger, et al., Proc. Natl. Acad. Science USA, vol. 85, Apr. 1988, pp. 2357-2361.
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Morrison, et al., Proc. Natl. Acad. Science, vol. 81, Nov. 1984, pp. 6851-6855.

Oi, Vernon T., Bio. Techniques, vol. 4, No. 3, 1986, pp. 214-220.

ART-UNIT: 185
PRIMARY-EXAMINER: Guzo; David
ATTY-AGENT-FIRM: Morgan & Finnegan

ABSTRACT:

A chimeric gene directing the synthesis of hybrid recombinant fusion protein in a suitable expression vector has been constructed. The fusion protein possesses the property of selective cytotoxicity against specific virus-infected cells. A CD4(178)-PE40 hybrid fusion protein has been made for selectively killing HIV-infected cells.

8 Claims, 10 Drawing figures

☐ 24. Document ID: US 5504000 A

L6: Entry 24 of 28 File: USPT Apr 2, 1996

US-PAT-NO: 5504000
DOCUMENT-IDENTIFIER: US 5504000 A

TITLE: Chimeric protein tyrosine kinases

DATE-ISSUED: April 2, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Littman; Dan	San Francisco	CA	N/A	N/A
Xu; Hua	San Francisco	CA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Regents of the University of California	Oakland	CA	N/A	N/A	02

APPL-NO: 8/ 459170
DATE FILED: June 2, 1995

PARENT-CASE:
This is a division of application Ser. No. 08/112,912 filed Aug. 27, 1993, now U.S. Pat. No. 5,439,812.

INT-CL: [6] C12N 9/12, C12N 5/00, C12P 21/06, C07H 19/00
US-CL-ISSUED: 435/194; 435/69.1, 435/69.7, 435/240.2, 530/350, 536/22.1, 536/23.1, 536/23.2, 536/23.4, 536/23.5
US-CL-CURRENT: 435/194; 435/69.1, 435/69.7, 530/350, 536/22.1, 536/23.1, 536/23.2, 536/23.4, 536/23.5
FIELD-OF-SEARCH: 435/69.1, 435/69.7, 435/194, 435/240.2, 530/350, 536/22.1, 536/23.1, 536/23.2, 536/23.4, 536/23.5

PRIOR-ART-DISCLOSED:

OTHER PUBLICATIONS

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Turner et al. "Unteraction of the Unique N-Terminal . . . " Cell 60:755-765 (1990).

ART-UNIT: 184
PRIMARY-EXAMINER: Wax; Robert A.
ASSISTANT-EXAMINER: Kim; Hyosuk
ATTY-AGENT-FIRM: Townsend and Townsend and Crew

ABSTRACT:

The present invention provides chimeric proteins containing extracellular and transmembrane domains of CD4 and protein tyrosine kinases of the src family. Also provided are DNA molecules encoding the proteins of the present invention and cells containing such DNA molecules. The proteins and cells of the present invention may be employed in methods for identifying drugs that block T cell activation and for identifying low level self-antigens.

5 Claims, 15 Drawing figures

☐ 25. Document ID: US 5439819 A

L6: Entry 25 of 28 File: USPT Aug 8, 1995

US-PAT-NO: 5439819
DOCUMENT-IDENTIFIER: US 5439819 A

TITLE: Chimeric protein tyrosine kinases

DATE-ISSUED: August 8, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Littman; Dan	San Francisco	CA	N/A	N/A
Xu; Hua	San Francisco	CA	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The Regents of the University of California	Oakland	CA	N/A	N/A	02

APPL-NO: 8/ 112912
DATE FILED: August 27, 1993

INT-CL: [6] C12N 5/00, C12N 9/12, C12P 21/06, C07H 19/00
US-CL-ISSUED: 435/240.2; 435/69.1, 435/69.7, 435/194, 530/350, 536/22.1, 536/23.1, 536/23.2, 536/23.4, 536/23.5
US-CL-CURRENT: 435/372.3; 435/194, 435/69.1, 435/69.7, 530/350, 536/22.1, 536/23.1, 536/23.2, 536/23.4, 536/23.5
FIELD-OF-SEARCH: 435/69.1, 435/69.7, 435/194, 435/240.2, 530/350, 536/22.1, 536/23.1, 536/23.2, 536/23.4, 536/23.5

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4929604	May 1990	Munford et al.	514/53

OTHER PUBLICATIONS

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Zamoyska et al., "Inability of CD8.alpha..varies. polypeptides to associate with p 56.sup.lck correlates with impaired function in vitro and lack of expression in vivo," Nature, 342:278-281 (1989).
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Shaw et al., "Short Related Sequences in the Cytoplasmic Dimains of CD4 and CD8 Mediate Binding to the Amino-Terminal Domain of the p 56.sup.lck Tyrosine Protein Kinase," Mol. Cell. Biol., 10:1853-1862 (1990).
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Weiss, "T Cell Antigen Receptor Signal Transduction: A Tale of Tails and Cytoplasmic Protein-Tyrosine Kinases," Cell, 73:209-212 (1993).
Feig, "The Many Roads That Lead to Ras," Science, 260:767-768 (1993).

ART-UNIT: 184
PRIMARY-EXAMINER: Wax; Robert A.
ASSISTANT-EXAMINER: Kim; Hyosuk
ATTY-AGENT-FIRM: Townsend and Townsend Khourie and Crew

ABSTRACT:

The present invention provides chimeric proteins containing extracellular and transmembrane domains of CD4 and protein tyrosine kinases of the src family. Also provided are DNA molecules encoding the proteins of the present invention and cells containing such DNA molecules. The proteins and cells of the present invention may be employed in methods for identifying drugs that block T cell activation and for identifying low level self-antigens.

7 Claims, 15 Drawing figures

☐ 26. Document ID: US 5428143 A

L6: Entry 26 of 28 File: USPT Jun 27, 1995

US-PAT-NO: 5428143
DOCUMENT-IDENTIFIER: US 5428143 A

TITLE: Cytotoxic agent against specific virus infection

DATE-ISSUED: June 27, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Berger; Edward A.	Rockville	MD	N/A	N/A
Moss; Bernard	Bethesda	MD	N/A	N/A
Fuerst; Thomas R.	Gaithersburg	MD	N/A	N/A
Pastan; Ira	Potomac	MD	N/A	N/A
Fitzgerald; David	Silverspring	MD	N/A	N/A
Mizukami; Tamio	Bethesda	MD	N/A	N/A
Chaudhary; Vijay K.	Rockville	MD	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
United States of America	Washington	DC	N/A	N/A	06

DISCLAIMER DATE: 20100427

APPL-NO: 8/ 022095
DATE FILED: February 25, 1993

PARENT-CASE:
This is a continuation of application Ser. No. 07/223,270 filed Jul. 22, 1988, now U.S. Pat. No. 5,206,353.

INT-CL: [6] C12N 15/62
US-CL-ISSUED: 536/23.4; 536/23.1, 536/23.5
US-CL-CURRENT: 536/23.4; 536/23.1, 536/23.5
FIELD-OF-SEARCH: 435/69.1, 435/69.7, 435/320.1, 536/23.1, 536/23.4, 536/23.5

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4545985	October 1985	Pastan et al.	424/180.1
4892827	January 1990	Pastan et al.	435/193
5206353	April 1993	Berger et al.	536/23.4

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO8903222	April 1989	WOX	
WO9004414	May 1990	WOX	

OTHER PUBLICATIONS

Chaudhary et al., Nature, vol. 335, No. 6188, 22nd Sep. 1988, pp. 369-372.
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Bedinger P., Nature, vol. 223, 14th Jul. 1988, pp. 162-165.
Chaudhary, et al., Proc. Natl. Acad. Sci., vol. 84, Jul. 1987, pp. 4538-4542.
McDougal, et al., Science, vol. 231, Jan. 1986, pp. 382-385.
Maddon, et al., Cell, vol. 42 Aug. 1985, pp. 93-104.
Berger, et al., Proc. Natl. Acad. Science USA, vol. 85, Apr. 1988, pp. 2357-2361.
Chakrabarti, et al., Nature, vol. 320, Apr. 1986, pp. 535-537.
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Oi, Vernon T., Bio. Techniques, vol. 4, No. 3, 1986, pp. 214-220.

ART-UNIT: 185
PRIMARY-EXAMINER: Schwartz; Richard A.
ASSISTANT-EXAMINER: Guzo; David
ATTY-AGENT-FIRM: Morgan & Finnegan

ABSTRACT:

A chimeric gene directing the synthesis of hybrid recombinant fusion protein in a suitable expression vector has been constructed. The fusion protein possesses the property of selective cytotoxicity against specific virus-infected cells. A CD4(178)-PE40 hybrid fusion protein has been made for selectively killing HIV-infected cells.

1 Claims, 10 Drawing figures

☐ 27. Document ID: US 5328984 A

L6: Entry 27 of 28 File: USPT Jul 12, 1994

US-PAT-NO: 5328984
DOCUMENT-IDENTIFIER: US 5328984 A

TITLE: Recombinant chimeric proteins deliverable across cellular membranes into cytosol of target cells

DATE-ISSUED: July 12, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira H.	Potomac	MD	N/A	N/A
Trevor; Prior	Bethesda	MD	N/A	N/A
Fitzgerald; David J.	Silver Spring	MD	N/A	N/A
Debinski; Waldemar	Gaithersburg	MD	N/A	N/A
Siegall; Clay	Silver Springs	MD	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY TYPE CODE
The United States as represented by the Department of Health & Human Services	Bethesda	MD		06

APPL-NO: 7/ 663455
DATE FILED: March 4, 1991

INT-CL: [5] C07K 13/00, C07K 15/04, A61K 37/02
US-CL-ISSUED: 424/134.1; 530/402, 530/399, 530/350, 530/387.3, 536/23.4, 435/69.7
US-CL-CURRENT: 424/134.1; 435/69.7, 530/350, 530/387.3, 530/399, 530/402, 536/23.4
FIELD-OF-SEARCH: 424/92, 424/85.91, 435/69.7, 514/12, 514/2, 530/350, 530/402, 530/391.7, 536/23.4

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4675382	June 1987	Murphy	530/350
4892827	January 1990	Pastan et al.	424/92
4933288	June 1990	Greenfield	435/69.5
5080898	January 1992	Murphy	424/94.6
5082927	January 1992	Pastan et al.	424/92
5084556	January 1992	Brown	424/85.91
5135736	August 1992	Anderson et al.	424/85.91
5169933	December 1992	Anderson et al.	424/85.91
5206353	April 1993	Berger et al.	435/69.7

OTHER PUBLICATIONS

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Hartley, "Barnase and Barstar", J. Mol. Biol. 202:913-915, 1988.
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Batra et al., "Anti-Tac (Fv)-PE40, a Single Chain Antibody Pseudomonas Fusion Protein . . . ", J. Biol. Chem. 265:15198-15202, Sep. 5, 1990.
Roberge et al., "Selective Immunosuppression of Activated T Cells . . . ", J. Immunol. 143:3498-3502, Dec. 1, 1989.
Prior et al, "Cytotoxic Activity of a Recombinant Fusion Protein . . . ", Cancer Res. 51:174-180, Jan. 1, 1991.
Debinski et al., "Substitution of Foreign Protein Sequences into a Chimeric Toxin . . . ", Mol. Cell. Biol. 11:1751-1753, Mar. 1991.
Siegall et al., "Cytotoxic Activity of an Interleukin 6-Pseudomonas exotoxin fusion protein . . . ", PNAS 85:9738-9742, Dec. 1988.

ART-UNIT: 184
PRIMARY-EXAMINER: Wax; Robert A.
ASSISTANT-EXAMINER: Walsh; Stephen
ATTY-AGENT-FIRM: Townsend and Townsend Khourie and Crew

ABSTRACT:

Proteins that are impermeable and foreign to the eukaryotic cells can now be delivered across cellular membranes into the cytosol of target cells by making a chimeric protein having specific attributes. A method of making such chimeric

proteins is disclosed. As an example, a chimeric protein PE-Bar with dual enzymatic activity has been made. The chimeric proteins can be used for cytotoxic, diagnostic or therapeutic purposes, such as for compensating the deficiency or defect of an enzyme or a protein which may be causative of a disease or an abnormality.

13 Claims, 8 Drawing figures

☐ 28. Document ID: US 5206353 A

L6: Entry 28 of 28 File: USPT Apr 27, 1993

US-PAT-NO: 5206353
DOCUMENT-IDENTIFIER: US 5206353 A

TITLE: CD-4/cytotoxic gene fusions

DATE-ISSUED: April 27, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Berger; Edward A.	Rockville	MD	N/A	N/A
Moss; Bernard	Bethesda	MD	N/A	N/A
Fuerst; Thomas R.	Gaithersburg	MD	N/A	N/A
Pastan; Ira	Potomac	MD	N/A	N/A
Fitzgerald; David	Silver Spring	MD	N/A	N/A
Mizukami; Tamio	Bethesda	MD	N/A	N/A
Chaudhary; Vijay K.	Rockville	MD	N/A	N/A

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The United States of America as represented by the Department of Health and Human Services	Washington	DC			06

APPL-NO: 7/ 223270
DATE FILED: July 22, 1988

INT-CL: [5] C12N 15/11
US-CL-ISSUED: 536/23.4; 435/69.7, 435/172.3, 435/320.1, 435/252.33
US-CL-CURRENT: 536/23.4; 435/252.33, 435/320.1, 435/69.7
FIELD-OF-SEARCH: 536/27, 435/172.3, 435/252.33, 435/320.1, 935/9, 935/29

PRIOR-ART-DISCLOSED:

OTHER PUBLICATIONS

Chaudhary, et al. Proc. Natl. Acad. Sci:USA 84:4538-4542, 1987.
McDougal, et al. Science 231:382-385, 1986.
Maddon, et al. Cell 42: 93-104, 1985.
Chakrabaty et al. Nature 320:535-537, 1986.

ART-UNIT: 185
PRIMARY-EXAMINER: Schwartz; Richard A.

ASSISTANT-EXAMINER: LeGuyader; J.
ATTY-AGENT-FIRM: NIH/Office of Technology Transfer

ABSTRACT:

A chimeric gene directing the synthesis of hybrid recombinant fusion protein in a suitable expression vector has been constructed. The fusion protein possesses the property of selective cytotoxicity against specific virus-infected cells. A CD4(178)-PE40 hybrid fusion protein has been made for selectively killing HIV-infected cells.

9 Claims, 10 Drawing figures

2,7,12

WEST

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☐ 1. Document ID: US 6255458 B1

L6: Entry 1 of 28 File: USPT Jul 3, 2001

DOCUMENT-IDENTIFIER: US 6255458 B1
TITLE: High affinity human antibodies and human antibodies against digoxin

DEPR:
The ability of a human anti-CD4 mAb to inhibit a T-helper cell dependent immune response in primates can be demonstrated by immunizing the primate with a soluble foreign antigen (e.g., tetanus toxoid (TT)) and measuring the ability of the primate to mount a delayed-type hypersensitivity reaction (DTH) to the antigen (e.g., following injection of the human mAb). The DTH is mediated by CD4.sup.+ (T-helper) cells (E. Benjamin and S. Lescowitz, Immunology: A Short Course, Second Edition, (1991) Wiley-Liss, Inc., New York, pp. 277-292). Antigen-specific T-helper cells recognize the processed antigen presented by MHC Class II molecules on antigen-presenting cells and become activated. The activated T-helper cells secrete a variety of lymphokines (IL2, INF.gamma., TNF.beta., MCF) and thus attract and activate macrophages and T-cytotoxic cells at the injection site. Although most of the effector functions occurring as part of the DTH are performed by macrophages and T-cytotoxic cells, it is the T-helper cells which initiate the response. Therefore, if the T-helper cells can be inhibited, there will be no DTH. Administration of anti-CD4 mABs has been shown to prevent (Wofsy, et al., J. Exp. Med., 161:378-391 (1985)) or reverse (Wofsy, et al., J. Immunol., 138:3247-3253 (1987), Waldor, et al., Science, 227:415-417 (1985)) autoimmune disease in animal models. Administration of murine or chimeric anti-CD4 mAbs to patients with rheumatoid arthritis has shown evidence of clinical benefit (Knox, et al., Blood, 77:20-30 (1991); Goldbery, et al., J. Autoimmunity, 4:617-630; Herzog, et al., Lancet, ii:1461-1462; Horneff, et al., Arthritis Rheum., 34:129-140; Reiter, et al., Arthritis Rheum., 34:525-536; Wending, et al., J. Rheum., 18:325-327; Van der Lubbe, et al., Arthritis Rheum., 38:1097-1106; Van der Lubbe, et al., Arthritis Rheum., 36:1375-1379; Moreland, et al., Arthritis Rheum., 36:307-318, and Choy, et al., Arthritis and Rheumatism, 39(1):52-56 (1996); all of which is incorporated herein by reference). In addition, as noted above, a chimeric anti-CD4 mAB has shown some clinical efficacy in patients with mycosis fungoides (Knox et al. (1991) Blood 77:20; which is incorporated herein by reference). Anti-CD4 antibodies are also discussed in Newman, et al., Biotechnology, 10:1455-1460 (1992), which is incorporated herein by reference.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6232445 B1

L6: Entry 2 of 28 File: USPT May 15, 2001

DOCUMENT-IDENTIFIER: US 6232445 B1
TITLE: Soluble MHC complexes and methods of use thereof

BSPR:
A polyspecific MHC complex of the invention generally includes one or more sc-MHC class I or class II molecules (the same or different) up to about two to five of such molecules. In accord with the present invention, the sc-MHC molecules can include a modified .beta.2 class II chain and/or a fused Ig-C.sub.L chain or suitable Ig-C.sub.L chain fragment to facilitate soluble expression of the complex. Exemplary polyspecific MHC complexes include class II complexes comprising one sc-MHC class II molecule sometimes comprising a modified .beta.2 class II chain. Additionally, chimeric polyspecific MHC complexes comprising one or more sc-MHC molecules of known classes (IA.sup.d, DR1, DR2, DP, IE, QP, etc.) are also within the scope of the present invention.

DEPR:
As mentioned above, a variety of polypeptides have been shown to form specific binding pairs. For example, coiled coils (such as a leucine zipper), helix-turn-helix polypeptide motifs and related structures have been shown to facilitate dimerization and oligomerization of single-chain antibody Fv fragments, the .alpha. and .beta. chain of T-cell receptor molecules, and the .alpha. and the .beta. chains of MHC class II molecules. See e.g., Pack et al., Biotechnology, 11:1271 (1993); Pack et al., J. Mol. Biol., 246:28 (1995); Chaing et al., Proc. Natl. Acad. Sci. USA91:11408 (1994); Scott et al., J. Exp. Med., 183:2087 (1996).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 6180377 B1

L6: Entry 3 of 28 File: USPT Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180377 B1
TITLE: Humanized antibodies

DEPR:
The principle of this assay is that if the antigen binding region has been correctly transferred from the murine to human frameworks, then the CDR grafted antibody will compete equally well with a labelled chimeric antibody for binding to human MHC Class II. Any changes in the antigen binding potency will be revealed in this system.

DEPR:
The ability of chimeric and CDR grafted L243 to suppress a secondary response was assessed using a recall response to Tetanus toxin. The principle of the experiment is that T lymphocytes from an individual previously immunised with Tetanus toxoid (TT) will respond to TT when re-exposed ex vivo. This activation is dependent on the interaction between the CD3/TcR complex on T cells and the MHC Class II molecules on cells which process and present the antigen. L243 is known to inhibit this reaction.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 4. Document ID: US 6103239 A

L6: Entry 4 of 28 File: USPT Aug 15, 2000

DOCUMENT-IDENTIFIER: US 6103239 A
TITLE: Modified HGP-30 heteroconjugates, compositions and methods of use

DETL:
TABLE 1 TCBL Peptides used in Heteroconjugate Construction Name/Amino Acid Sequence Molecule/a.a. positions MHC Class I MHC-I.sub..alpha.3 DQT QDT E 223-229 (SEQ ID NO:51) Lymphokine IL-1.sub..beta. VQG EES NDK 163-171 (SEQ ID NO:52) MHC Class II MHC-II.sub..beta.2 NGQ EEK AGV VST GLI 135-149 (SEQ ID NO:53) .beta.-2-Microglobulin .beta.-2-M DLL KNG ERI EKV E 35-47 (SEQ ID NO:54)

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 5. Document ID: US 6060309 A

L6: Entry 5 of 28 File: USPT May 9, 2000

DOCUMENT-IDENTIFIER: US 6060309 A
TITLE: Immune mediators and related methods

BSPR:
An ELISA (Enzyme-linked Immunosorbent Assay) can be used to measure concentration and confirm correct folding of the soluble, fused heterodimer molecules. This assay can be used with either whole cells, solublized MHC, removed from the cell surface; or free soluble, fused heterodimer molecules of the current invention. In an exemplary ELISA, an antibody that detects the recombinant MHC haplotype is coated onto wells of a microtiter plate. In a preferred embodiment, the antibody is L243, a monoclonal antibody that recognizes only correctly folded HLA-DR MHC dimers. One of skill in the art will recognize that other MHC Class II-specific antibodies are known and available. Alternatively, there are numerous routine techniques and methodologies in the field for producing antibodies (for example, Hurrell, J. G. R. (ed)., Monoclonal Hybridoma Antibodies: Techniques and Applications, CRC Press Inc., Boca Raton, Fla., 1982), if an appropriate antibody for a particular haplotype does not exist. Anti-MHC Class II antibodies can also be used to purify Class II antibodies can also be used to purify Class II molecules through techniques such as affinity chromatography, or as a marker reagent to detect the presence of Class II molecules on cells or in solution. Such antibodies are also useful for western analysis or immunoblotting, particularly of purified cell secreted material. Polyclonal, affinity purified polyclonal, monoclonal and single chain antibodies are suitable for use in this regard. In addition, proteolytic and recombinant fragments and epitope binding domains can be used herein. Chimeric, humanized, veneered, CDR-replaced, reshaped or other recombinant whole or partial antibodies are also suitable.

☐ 6. Document ID: US 6022863 A

L6: Entry 6 of 28 File: USPT Feb 8, 2000

DOCUMENT-IDENTIFIER: US 6022863 A
TITLE: Regulation of gene expression

BSPR:
The mechanism of IFN-.gamma.-induced MHC gene expression has been elucidated by numerous studies of the molecules involved, including the subunits of the IFN-.gamma. receptor (Aguet et al., 1988, Cell 55:273-280; Hemmi et al., 1994, Cell 76:803-10; Soh et al., 1994, Cell 76:793-802), Jak kinases and the STAT transcription factors (Darnell et al., 1994, Science 264:1415-20), the interferon stimulated response elements (ISRE) conserved in MHC class I (Vallejo and Pease, 1995, Immunol. Rev. 143:249-262; Le Bouteiller, 1994, Crit. Rev. Immunol. 14:89-129) and other genes, and the gamma-interferon activation site (GAS) elements conserved in other IFN-.gamma.-responsive genes (Darnell et al., 1994, Science 264:1415-20) such as ICAM-1, B7-1, B7-2 and Fc.gamma.R genes. The following cellular events have been established in the Jak-STAT pathway of IFN-.gamma. signaling. Jak1 binds to the cytoplasmic domain of the IFN-.gamma. receptor .alpha.-subunit. Binding of IFN-.gamma. dimer to the extracellular domain of the dimerized .alpha.-subunit leads to association with IFN-.gamma. receptor .beta.-subunits and binding of Jak2 to the cytoplasmic domain of the .beta.-subunit. Phosphorylation of tyrosine residues by Jak1 and Jak2 on the kinases and the receptor .alpha.-subunits stimulates recruitment of STAT1 to the receptor (Kotenko et al., 1995, J. Biol. Chem. 270:20915-921; Sakatsume et al., 1995, J. Biol. Chem. 270:17528-534). Phosphorylation of STAT1 on tyrosine causes dimerization and transport to the nucleus (Shuai et al., 1993, Science 261:1744-46; Greenlund et al., 1995, Immunity 2:677-687) for trans-activation of IFN-.gamma.-responsive genes. Expression of MHC class I genes is induced by STAT1-containing transcription factors that bind ISRE sequences and can be enhanced by tumor necrosis factor-.alpha.-mediated activation of NF-.kappa.B transcription factors that bind neighboring .kappa.B sites (Thanos and Maniatis, 1995, Cell 80:529-32). Stimulation of MHC class II gene expression by IFN-.gamma. is initiated by Jak-STAT activation, but also requires the de novo production of the CIITA factor (Steimle et al., 1993, Cell 75:135-146; Steimle et al., 1994, Science 265:106-109; Chang et al., 1994, J. Exp. Med. 180:1367-74) which interacts with constitutively expressed DNA-binding proteins on conserved promoter sequences in MHC class II genes (Glimcher and Kara, 1992, Annu. Rev. Immunol. 10:13-49). Jak-STAT activation has also been implicated in activation of gene transcription by other cytokines such as interferon-.alpha., interferon-.beta., granulocyte colony stimulating factor, epidermal growth factor, growth hormone, ciliary neurotrophic factor, prolactin, leukemia inhibitory factor, interleukin-2, interleukin-3, interleukin-4, interleukin-5, interleukin-6, interleukin-8, interleukin-10, interleukin-13, and interleukin-15. (Ihle and Kerr, 1995, Trends in Genetics 11:69-73; Darnell et al., 1994, Science 264:1415-20.)

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 7. Document ID: US 6015884 A

L6: Entry 7 of 28 File: USPT Jan 18, 2000

DOCUMENT-IDENTIFIER: US 6015884 A
TITLE: Soluble divalent and multivalent heterodimeric analogs of proteins

DEPR:
DNA constructs encoding the chimeric compounds of the present invention generally comprise sequences coding for the signal sequence and extracellular domain of one polypeptide of the heterodimeric complex (i.e. TCR.alpha. or .beta., or MHC class II .alpha. or .beta.) fused to the first amino acid of either the heavy or light chain immunoglobulin variable region sequence. Such a DNA construct results in the expression and secretion of a protein comprising the extracellular portion of the polypeptide of interest at the N terminus (transmembrane regions are not included) spliced to the intact variable region of the immunoglobulin molecule (see FIG. 1). Variations or truncations of this general structure in which one or more amino acids are inserted or deleted but which retain the ability to bind to the target ligand are encompassed in the present invention.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 8. Document ID: US 5969109 A

L6: Entry 8 of 28 File: USPT Oct 19, 1999

DOCUMENT-IDENTIFIER: US 5969109 A
TITLE: Chimeric antibodies comprising antigen binding sites and B and T cell epitopes

DEPR:
A chimeric immunoglobulin molecule carrying a HA T.sub.h epitope was prepared (Zaghouani et al., 1993, Science 259:224-227) using methods analogous to those set forth above. The 5.5 kb DNA fragment encoding the heavy chain variable region ("V.sub.H ") of the 91A3 antibody was used in PCR mutagenesis (Zaghouani et al., 1992, J. Immunol. 148: 3604) to replace the D segment with a nucleotide sequence encoding a T.sub.h epitope of the HA of PR8 influenza virus. This epitope corresponds to amino acid residues 110 to 120 of HA and is recognized by CD4.sup.+ T cells in association with I-E.sup.d MHC class II molecules. The mutated VH gene, from which the D segment was deleted and the cognate peptide sequence inserted in the correct frame, was subcloned in a pSV2gpt vector upstream of the exons of the BALB/c gamma 2b constant region from which the MOPC 141 VDJ fragment had been excised. To express this gene with the homologous light chain gene, the vector was transfected into the non-Ig-secreting BALB/c myeloma B cell line SP2/0, together with a pSV2-neo vector carrying the rearranged 91A3 light chain gene. The resulting antibody was termed "Ig-HA".

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 9. Document ID: US 5908762 A

L6: Entry 9 of 28 File: USPT Jun 1, 1999

DOCUMENT-IDENTIFIER: US 5908762 A
TITLE: Transcription factor regulating MHC expression CDNA and genomic clones encoding same and retroviral expression constructs thereof

ORPL:
Reith, et al., "MHC class II regulatory factor RFX has a novel DNA-binding domain and a functionally independent dimerization domain," Genes & Dev., 4:1528-1540 (1990).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

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☐ 10. Document ID: US 5906928 A

L6: Entry 10 of 28 File: USPT May 25, 1999

DOCUMENT-IDENTIFIER: US 5906928 A
TITLE: Efficient gene transfer into primary murine lymphocytes obviating the need for drug selection

DEPR:
As discussed in the Examples, infra, vectors for transfection of an autoantigen in B cells can be prepared so that the autoantigen is expressed intracytoplasmically, for transport via the endogenous cellular machinery for presentation in the context of MHC class II molecules (e.g., Braciale and Braciale, 1991, Immunol. Today 12:124; Brodsky and Guagliardi, 1991, Ann. Rev. Immunol. 9:707). More preferably, the autoantigen can be expressed as a secreted protein or a cell surface protein, by including a signal sequence, and, in the latter case, a membrane-binding sequence. In another preferred embodiment, the autoantigen is expressed as a chimeric construct, with an endosomal or lysosomal targeting sequence at the cytoplasmic end (Braciale and Braciale, supra; Brodsky and Guagliardi, supra; Peters et al., 1990, EMBO J. 9:3497; Bakke and Dobberstein, 1990, Cell 63:707).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

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☐ 11. Document ID: US 5876708 A

L6: Entry 11 of 28 File: USPT Mar 2, 1999

DOCUMENT-IDENTIFIER: US 5876708 A
TITLE: Allogeneic and xenogeneic transplantation

DEPR:
Overwhelming importance of major histocompatibility complex (MHC) class II matching for achieving tolerance of kidney transplants (KTx) in miniature swine has been demonstrated previously. When class II antigens are matched, long-term specific tolerance across MHC class I and minor antigens (MA) barrier, can uniformly be induced by a short course of cyclosporine. However, cyclosporine does not produce this effect across a full MHC barrier. Bone marrow transplantation (BMT) across single-haplotype class II MHC+MA barriers creates fully chimeric animals, as confirmed by FCM. These chimeras recover normal cellular immune function 2-3 months after BMT, as tested by MLR and CML. Four such chimeric animals (see Table 1, numbers 1-4) received kidney transplants from donors class II matched to BMT donors and fully mismatched to the recipients. A 12-day course of cyclosporine (10 mg/kg/day) was the only immunosuppression following kidney transplantation. All 4 pigs have maintained normal creatinine (Cr) values (<2 mg%) for longer than 300 days, and one recipient is alive over 3 years with good kidney function (Cr<2 mg%) and graft histology showing minimal borderline rejection. These results demonstrate that induction of tolerance to class II antigens by BMT allows a short course of cyclosporine to induce specific tolerance (as tested by skin grafts) to fully allogeneic kidney transplants. Subsequently, we have examined the specificity of this phenomenon by determining if single-haplotype class II+MA mismatched BMT will facilitate cyclosporine induced long-term acceptance of kidney transplants completely mismatched to both the recipient and BMT donor (Table 1, numbers 5-10). A 12-day course of cyclosporine allowed long-term survival of such kidney transplants in chimeric recipients. Animal #5 was still alive and clinically well, with normal Cr levels; histology however reveals borderline rejection. Animal #6 was sacrificed 18 months after kidney transplant, with deteriorating kidney function (Cr>11 mg%). Animal #7 was sacrificed at 6 months after kidney transplant due to sepsis, kidney transplants showed moderate tubulointestinal infiltrate without signs of vascular injury. Both long-term survivors (pigs #3 & 5) were recently tested for anti-donor reactivity. CML and MLR revealed specific unresponsiveness to the kidney transplant donor type cells. Pigs #8-10 received kidney transplant from outbred Yorkshire donors. These animals developed irreversible renal failure, starting shortly after cessation of the cyclosporine therapy.

☐ 12. Document ID: US 5869270 A

L6: Entry 12 of 28 File: USPT Feb 9, 1999

DOCUMENT-IDENTIFIER: US 5869270 A
TITLE: Single chain MHC complexes and uses thereof

DEPR:
With respect to the full length MHC complexes (both single chain and non-single chain molecules) the MHC proteins can be anchored to cell membranes through hydrophobic membrane spanning domains (transmembrane domains) as well as through post-translational attachment of the covalently linked glycosylated form of phosphatidylinositol (GPI membrane anchor). Typically for the .alpha. and .beta. chains of the MHC class II molecule, the transmembrane domain consists of approximately 25 hydrophobic amino acids connected to the carboxyl terminal side of the .alpha.2 and .beta.2 domains. These residues allow the protein to span the membrane. The transmembrane region ends with about 10-15 residues comprising the cytoplasmic tail at the carboxyl terminal end of each of these chains. It has been demonstrated that these transmembrane and cytoplasmic regions can be replaced with sequences signaling GPI linkage and that the chimeric GPI-anchored class II molecules are membrane bound [D. Wettstein et al., J. Exp. Med., 174:219-228 (1991)]. GPI-linked membrane anchor domains have been defined in a number of proteins including decay accelerating factor (DAF), CD59 and humans placental alkaline phosphatase (HPAP) [D. Wettstein et al., J. Exp. Med., 174:219-228 (1991); D. Kooyman et al.]. For example, the 38 carboxyl terminal amino acids of HPAP are sufficient to act as a signal sequence for GPI linkage. If the DNA sequence encoding this domain is linked to a secreted molecule such as the soluble portion of the MHC class II .alpha. or .beta. chain, a membrane bound chimeric molecule is formed [D. Wettstein et al., J. Exp. Med., 174:219-228 (1991)], and such an approach can be employed to anchor peptide-linked single chain class II MHC molecules to a cell membrane.

DEPR:
The following protocol includes expression of soluble peptide-linked MHC class II/immunoglobulin molecules as chimeric protein. The objective is to construct an antibody-like molecule that has kappa constant domain plus the MHC class II .alpha. chain region and the murine IgG2b constant domain joined with the MHC class II .beta. chain covalently linked to peptides of interest. These constructs are then cloned into separate mammalian expression vectors and used to transfect lymphoid derived cell lines, i.e. J558.

DEPR:
The MHC class II genes used for these constructs were originally isolated by PCR amplification of cDNA generated from the appropriate APC as described in the above examples (see in particular Example 1 above). Fragments of the I-A.sup.d .alpha. and .beta. chain genes were generated by PCR amplification using cloned genes as template DNA and were assembled in the cloning scheme shown in FIG. 25 of the Drawings resulting in a chimeric gene encoding the antigenic peptide, OVA 323-339, linked to a single-chain I-A.sup.d molecule. Briefly, the .alpha.1-.alpha.2 gene fragment cloned into 39AD2 served as the template for PCR amplification using primers JLA007 and JLA010 (all of the oligonucleotides used in cloning are listed in FIG. 26 of the Drawings), resulting in the addition of a 5' XhoI and a 3' XmaI restriction site. The .alpha.1-.alpha.2 PCR product was digested with XhoI and XmaI, gel-purified and subcloned into the pLL101 vector resulting in the pJA.alpha.9 construct. This vector adds sequence encoding a 6xHis tag to the end of the .alpha.1-.alpha.2 protein to aid in protein to aid in protein purification.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

☐ 13. Document ID: US 5866760 A

L6: Entry 13 of 28 File: USPT Feb 2, 1999

DOCUMENT-IDENTIFIER: US 5866760 A
TITLE: Stat6 deficient transgenic mice

BSPR:
Signal transducers and activators of transcription (Stat) proteins are a recently identified class of transcription factors responsible for mediating may cytokine-induced responses. These proteins exist in a latent form in the cytoplasm and become phosphorylated by the Janus kinase (JAK) family of tyrosine kinases following cytokine-receptor interactions. Once phosphorylated, Stat proteins dimerize, translocate to the nucleus, and bind to specific DNA sequences to regulate gene transcription (Ihle, 1995; Schindler and Darnell, 1995). Of the presently know Stat proteins, only Stat6 is activated in response to the cytokine interleukin-4 (IL-4) (Kotanides and Reich, 1993; Hou et al, 1994; Schindler et al, 1994; Quelle et al., 1995). IL-4 is secreted by several cell types including stimulated T lymphocytes, mast cells, and basophils (Howard et al., 1982; Lee et al, 1986; Paul and Ohara, 1987; Yoshimoto and Paul, 1994; Sad et al., 1995). While initially identified by its ability to support the growth and differentiation of B lymphocytes costimulated with submitogenic doses of anti-immunoglobulin (Howard et al., 1982), IL-4 is now known to have pleiotropic effects on the immune system. IL-4 is essential for the induction of immunoglobulin E (IgE) synthesis by activated B lymphocytes and influences class switching to IgG1 as well (Vitetta et al, 1985; Coffman et al., 1986). B cells stimulated with IL-4 increase their cell surface expression of major histocompatibility complex (MHC) class II molecules (Noelle et al., 1984), IL-4 receptor (IL-4R) (Ohara and Paul, 1988), and the low affinity IgE receptor CD23 (Conrad et al., 1987). IL-4 also induces the proliferation of T lymphocytes and is important for the differentiation of T helper 2 (Th2) cells (Le Gros et al., 1990; Swain et al., 1990). Indeed, the analysis of IL-4-deficient mice generated by gene targeting in embryonic stem (ES) cells has confirmed the importance of this cytokine in mediating many of these responses (Kuhn et al., 1991; Kopf et al., 1993).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 14. Document ID: US 5859226 A

L6: Entry 14 of 28 File: USPT Jan 12, 1999

DOCUMENT-IDENTIFIER: US 5859226 A
TITLE: Polynucleotide decoys that inhibit MHC-II expression and uses thereof

ORPL:
Reith, W. et al., "MHC class II regulatory factor RFX has a novel DNA-binding domain and a functionally independent dimerization domain" Genes Dev. (1990) 4(9):1528-1540.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 15. Document ID: US 5840832 A

L6: Entry 15 of 28 File: USPT Nov 24, 1998

DOCUMENT-IDENTIFIER: US 5840832 A
TITLE: Transcription factor regulating MHC expression, CDNA and genomic clones encoding same and retroviral expression constructs thereof

ORPL:
Reith, et al., "MHC class II regulatory factor RFX has a novel DNA-binding domain and a functionally independent dimerization domain," Genes & Dev., 4:1528-1540 (1990).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 16. Document ID: US 5824315 A

L6: Entry 16 of 28 File: USPT Oct 20, 1998

DOCUMENT-IDENTIFIER: US 5824315 A
TITLE: Binding affinity of antigenic peptides for MHC molecules

DEPR:
Protein effector components can be conjugated to the MHC Class II component or peptide by standard dehydration reactions using carbodiimides. Heterobifunctional linkers such as SPDP, glutaraldehyde and the like can also be used.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 17. Document ID: US 5756096 A

L6: Entry 17 of 28 File: USPT May 26, 1998

DOCUMENT-IDENTIFIER: US 5756096 A
TITLE: Recombinant antibodies for human therapy

DEPR:
In a particularly preferred embodiment, the invention provides a specific recombinant referred to as CE9.1 (see Example 3) primate/human chimeric monoclonal antibody which is directed against the human CD4 antigen. This recombinant antibody has particular utility as an immunosuppressant and is especially useful for the treatment of autoimmune diseases such as rheumatoid arthritis. As described in greater detail in the Examples, in particular Example 3, this recombinant antibody is generated by grafting the antigen binding variable Fv domains from cynomolgus macaque to human constant IgG.sub.1 and gamma domains. More particularly, this antibody contains a human gamma 1 domain. The resultant recombinant antibody sequences are indistinguishable from human immunoglobulin sequences. As a result, this antibody upon in vivo administration in humans should exhibit reduced immunogenicity and longer serum half-life compared to similar murine monoclonal or mouse-human chimeric antibodies directed to CD4. This antibody binds to domain 1 of human, but not macaque, CD4, a region which is involved in the interaction with MHC Class II molecules on antigen presenting cells. Potent immunomodulatory activity has been observed with this antibody both in vitro and in vivo. Given these properties, i.e., reduced immunogenicity, longer half-life and potent immunosuppression, indicate that this antibody should be particularly suitable for long term therapy of diseases where immunosuppression is desirable, e.g., autoimmune disorders and chronic inflammatory diseases such as rheumatoid arthritis. However, it is expected that this antibody should be useful for the treatment of many other disease conditions including, by way of example, Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis/Graves disease, pernicious anaemia, autoimmune atrophic gastritis, autoimmune carditis, Addison's disease, premature menopause, type I-diabetes mellitus, Good pasture's syndrome, myasthenia gravis, multiple sclerosis, male infertility, pemphigus vulgaris, pemphigoid, sympathetic ophthalmia, phacogenic uveitis, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis (HBs Ag negative), cryptogenic cirrhosis, inflammatory bowel disease syndrome, Sjogren's syndrome, psoriasis, rheumatoid arthritis, dermatomyositis, scleroderma, mixed tissue connective disease, discoid lupus erythematosus, systemic vasculitis, and systemic lupus erythematosus (SLE). In the preferred embodiment, however, the disease indication will comprise rheumatoid arthritis.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 18. Document ID: US 5698679 A

L6: Entry 18 of 28 File: USPT Dec 16, 1997

DOCUMENT-IDENTIFIER: US 5698679 A
TITLE: Product and process for targeting an immune response

DEPR:
The secreted OVA.sub.326-337 chimeric light chain present in the supernatants of SP2/0 transfectomas were tested for their ability to be processed and presented by an antigen presenting cell (APC) in such a manner that the presented antigen could stimulate OVA peptide specific T cells. Two T cell hybridomas that express T cell receptors (TCR) capable of binding to MHC class II complexed with OVA peptides and secrete IL-2 upon stimulation were chosen. The TCR on hybridoma 3D0.54.8 can bind to MHC class II molecules complexed with OVA.sub.326-336 peptides. The TCR on hybridoma, D0.11.10/54.4 can bind to MHC class II molecules complexed with OVA.sub.323-336 peptides for optimal stimulation and OVA.sub.326-336 for poor stimulation.

☐ 19. Document ID: US 5670324 A

L6: Entry 19 of 28 File: USPT Sep 23, 1997

DOCUMENT-IDENTIFIER: US 5670324 A
TITLE: Use of chimeric CD4-src protein tyrosine kinases in drug screening and detection of an immune response

DEPR:
The CD4 chimeric proteins of the present invention may replace wild-type CD4 as a co-receptor during T cell activation. Association of CD4 extracellular and transmembrane domains with an src tyrosine kinase provides a means to mediate the function of the CD4 cytoplasmic domain in this system. The activity of the chimera required a functional CD4 extracellular domain as the chimeric protein are generally sensitive to mutations in the putative MHC class II binding site of CD4 and may be completely blocked by antibodies against CD4.

DEPR:
Infected cells were sorted to establish a polyclonal cell line expressing the chimeric protein. The same approach was used to prepare cell lines expressing the other constructs described below. The CD4+ cell lines were then tested for their response to stimulation with the antigen, a synthetic peptide analog of hen egg lysozyme, in the presence of antigen-presenting cells expressing the appropriate class II molecule, I-A.sup.b. FIG. 3A illustrates a comparison of responses of T cells expressing no CD4 (the parental 171.3 cells), the CD4/lck chimeric molecule (CtmLck), wild type CD4, mutant CD4 (MCA1) that does not bind p56.sup.lck, and mutant CD4 (MM4) or CD4/lck chimera (CtmLckMM4) that do not bind MHC class II. The T cells were stimulated by co-culturing with the appropriate antigen presenting cells and the peptide antigen at indicated concentrations.

DEPR:
Activated forms of src family kinases can increase IL-2 responses in the absence of a co-receptor interaction with ligand. For example, overexpression of an activated form of Lck has been previously shown to enhance responsiveness of a CD4- T cell hybridoma to stimulation with antigen (Abraham et al., Nature, 350:62-66 (1991). In addition, expression of viral src in another T cell line resulted in constitutive IL-2 expression (O'Shea et al., 1991). In order to rule out the possibility that the mode of action of the CD4/lck chimera was through constitutive activity of the PTK that lowered the

CD4/lck chimera was through constitutive activity of the TK that lowered the threshold for activation, the reported MHC class II binding site of CD4 (Lamarre et al., Science, 245:743-746 (1989); Clayton et al., Nature, 339:548-551 (1989), both of which are incorporated herein by reference) was mutated and assayed for functional activity. This mutation completely abolished the function of both CD4 and the CD4/lck chimera (CD4MM4 and CtmLckMM4 in FIG. 3A). The defect in these molecules was confined to the function of the extracellular domain, since antibody-mediated crosslinking of CD3 and the mutant CD4 or CD4/lck chimera resulted in normal levels of tyrosine phosphorylation of cellular substrates and the in vitro kinase activity of the MHC-non-binding mutant chimeric molecule was similar to that of the CtmLck molecule. In addition, the activity of the chimeric molecule in the T cell hybridoma was completely blocked by antibody against CD4 but not by a control MAb against .beta..sub.2 -microglobulin used as a control (FIG. 3B). These results indicate that, like wild type CD4, a functional class II-binding extracellular domain is essential for the activity of the CD4/lck hybrid molecule and confirms that this molecule is appropriately regulated in the 171.3 hybridoma.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 20. Document ID: US 5667998 A

L6: Entry 20 of 28 File: USPT Sep 16, 1997

DOCUMENT-IDENTIFIER: US 5667998 A
TITLE: Efficient gene transfer into primary lymphocytes obviating the need for drug selection

DEPR:
As discussed in the Examples, infra, vectors for transfection of an autoantigen in B cells can be prepared so that the autoantigen is expressed intracytoplasmically, for tramport via the endogenous cellular machinery for presentation in the context of MHC class II molecules (e.g., Braciale and Braciale, 1991, Immunol. Today 12:124; Brodsky and Guagliardi, 1991, Ann. Rev. Immunol. 9:707). More preferably, the autoantigen can be expressed as a secreted protein or a cell surface protein, by including a signal sequence, and, in the latter case, a membrane-binding sequence. In another preferred embodiment, the autoantigen is expressed as a chimeric construct, with an endosomal or lysosomal targeting sequence at the cytoplasmic end (Braciale and Braciale, supra; Brodsky and Guagliardi, supra; Peters et al., 1990, EMBO J. 9:3497; Bakke and Dobberstein, 1990, Cell 63:707).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 21. Document ID: US 5644065 A

L6: Entry 21 of 28 File: USPT Jul 1, 1997

DOCUMENT-IDENTIFIER: US 5644065 A
TITLE: Genetically engineered mice containing alterations in the MHC class II genes

ABPL:
The present invention provides mice which are deficient in the normal expression of one or more MHC class II genes, to mice heterozygous for such deficiency, and to cell lines, preferably pluripotent or totipotent cell lines, which are heterozygous, homozygous or chimeric for such deficiency, as well as to the use of any of the above, especially in situations where the absence of at least one MHC gene, or the normal expression thereof, is desirable.

BSPR:
The present invention relates to the fields of immunology and transgenic mice. Specifically, the present invention relates to mice which are deficient in the normal expression of one or more wild-type MHC class II genes, to mice heterozygous for such deficiency, and to cell lines, preferably pluripotent or totipotent cell lines, which are heterozygous, homozygous or chimeric for such deficiency.

DEPR:
The present invention provides mice which are deficient in the normal expression of one or more MHC class II genes, mice heterozygous for such deficiency, and cell lines, preferably pluripotent or totipotent cell lines, which are heterozygous, homozygous or chimeric for such deficiency, as well as to the use of any of the above, especially in situations where the absence of at least one MHC gene, or the normal expression thereof, is desirable.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 22. Document ID: US 5633234 A

L6: Entry 22 of 28 File: USPT May 27, 1997

DOCUMENT-IDENTIFIER: US 5633234 A
TITLE: Lysosomal targeting of immunogens

ABPL:
The inventors have discovered a targeting signal that will direct proteins to the endosomal/lysosomal compartment, and they have demonstrated that chimeric proteins containing a luminal antigenic domain and a cytoplasmic endosomal/lysosomal targeting signal will effectively target antigens to that compartment, where the antigenic domain is processed and peptides from it are presented on the cell surface in association with major histocompatibility (MHC) class II molecules. Chimeric DNA encoding the antigen of interest, linked to an endosomal/lysosomal targeting sequence, inserted in an immunization vector, can introduce the chimeric genes into cells, where the recombinant antigens are expressed and targeted to the endosomal/lysosomal compartment. As a result, the antigens associate more efficiently with MHC class II molecules, providing enhanced in vivo stimulation of CD4.sup.+ T cells specific for the recombinant antigen. Delivering antigens to an endosomal/lysosomal compartment by means of chimeric constructs containing such lysosomal targeting signals will be of value in any vaccination or immunization strategy that seeks to stimulate CD4.sup.+ MHC class II restricted immune responses.

BSPR:
In one embodiment, this invention provides a vaccine composition for eliciting an immune response in a mammal to an antigen, comprising a vaccine vector, wherein the vector contains a chimeric DNA segment which encodes a protein containing (1) an N-terminal domain containing a sequence encoding at least one epitope of said antigen, (2) a transmembrane domain and (3) a cytoplasmic domain containing an endosomal/lysosomal targeting signal directing the protein to the lysosomal membrane. In particular embodiments, the protein encoded by the chimeric DNA segment contains an intraluminal N-terminal domain comprising at least one epitope which is a peptide that complexes with major histocompatibility complex (MHC) class II molecules, and the protein has a short cytoplasmic domain which contains an endosomal/lysosomal targeting sequence near the C-terminus of the protein, the targeting sequence comprising the tetrapeptide sequence Tyr-Xaa-Xaa-Xbb, wherein Xbb is a hydrophobic amino acid.

BSPR:
This invention is based on the inventors' discovery of a targeting signal that will direct proteins to the endosomal/lysosomal compartment, and their discovery that chimeric transmembrane proteins containing a luminal antigenic domain and a cytoplasmic endosomal/lysosomal targeting signal will effectively target antigens to the endosomal/lysosomal compartment in which antigen processing and association with MHC class II occurs. These findings directly support the concept of including chimeric genes involving the antigen of interest, linked to an endosomal/lysosomal targeting sequence such as that of LAMP-1, in various immunization vectors. When these vectors introduce the chimeric genes into cells, the recombinant antigens are expressed and targeted to the endosomal/lysosomal compartment where they associate more efficiently with MHC class II molecules, resulting in enhanced in vivo stimulation of CD4.sup.+ T cells specific for the recombinant antigen. This represents a novel mechanism for targeting of protein antigens to the MHC class II pathway for presentation--a mechanism that will be more efficient than the earlier immunization strategies. The strategy of delivering antigens to an endosomal/lysosomal compartment by means of chimeric constructs containing such lysosomal targeting signals will be of value in any vaccination or immunization strategy that seeks to stimulate CD4.sup.+ MHC class II restricted immune responses.

DEPR:
The present invention provides immune stimulatory constructs composed of (1) an antigenic polypeptide domain containing one or more peptide segments which, when released by proteolytic enzymes, will complex with MHC class II molecules; (2) a transmembrane domain, and (3) a cytoplasmic tail containing an endosomal/lysosomal targeting signal that targets the antigenic domain to the compartment capable of antigen processing and presentation to MHC class II molecules. It further provides heterologous or chimeric DNA encoding such constructs which also contain appropriate control sequences followed in order by: a translation initiation site in reading frame with a signal sequence that will direct expression to the secretory compartment, the antigenic domain, a hydrophobic transmembrane domain, the cytoplasmic tail containing the endosomal/lysosomal targeting signal and a translational stop signal. Replicons containing this heterologous DNA are also provided by this invention.

DEPR:
Any sequences may be used which contain a signal that confers endosomal/lysosomal targeting. Examples of such sequences occur in the cytoplasmic domains of various lysosomal/endosomal membrane glycoproteins and receptors which cycle between endosomes and the plasma membrane. Sequences containing the targeting signal may be identified by constructing a chimeric DNA containing the antigenic domain of HA, a transmembrane domain, and the cytoplasmic domain of a protein containing a putative lysosomal/endosomal targeting signal. Efficiency of targeting is measured by the ability of antigen presenting cells, expressing the chimeric protein, to stimulate HA epitope specific, MHC class II restricted T-cells (see, e.g., Example 5

below).

DEPR:
In a particularly preferred embodiment, the invention provides a method of treatment for a cancer patient having low tumor burden, such as early in the disease, after resection of a neoplastic tumor, or when the burden of tumor cells is otherwise reduced. In this method, once a tumor-specific cell surface antigen characteristic of the patient's tumor has been identified, a cell population containing autologous stem cells capable of differentiation into antigen presenting cells which will express MHC class II molecules is obtained from the patient. These cells are cultured and transformed by introducing a heterologous or chimeric DNA molecule which encodes a protein containing (1) an N-terminal domain containing at least one epitope of the tumor-specific antigen found on the cells of the patient's tumor, (2) a transmembrane domain and (3) a cytoplasmic domain containing an endosomal/lysosomal targeting signal directing the protein to the lysosomal membrane, i.e., the DNA encodes the immune stimulatory construct described above. The transfected stem cell population is then reintroduced into the patient, where the stem cells differentiate into antigen presenting cells which express MHC class II molecules complexed with T.sub.h epitopes from the tumor-specific antigen. The immune response to the tumor-specific antigen will be enhanced by enhanced stimulation of the helper T cell population.

DEPR:
The system utilized to evaluate the strategy for MHC class II restricted antigen presentation of chimeric proteins with the LAMP lysosomal targeting signal uses the model antigen, influenza hemagglutinin (HA). HA is known to contain a number of helper T cell epitopes in various strains of mice. In particular, the amino acid fragment 111-120 represents a major helper epitope restricted by the MHC class II element I-E.sup.d in strains of mice such as BALB/c and DBA-2.

DEPR:
Specific MHC class II restricted T cell responses to these HA-LAMP constructs were assayed using a T cell receptor transgenic mouse in which the rearranged .alpha. and .beta. chains derived from a T cell clone specific for HA 111-120 plus I-E.sup.d have been inserted into the murine germ line. In these mice, roughly 20% of the CD4.sup.+ T cells express the HA specific T cell receptor; therefore, naive lymph node or splenic lymphocyte populations will respond by lymphokine secretion and proliferation when presented with the HA 111-120 by APCs expressing I-E.sup.d. The I-E.sup.d +B-cell lymphoma, A20 was used as an antigen presenting cell. Previous work demonstrated that when lysates from tumor cells expressing HA were fed to A20 cells, the HA protein was taken up and processed by the A20 cells and presented to T cells from the HA specific transgenic mice. A20 cells were stably transfected with one of two constructs: (1) wild-type HA and (2) a chimeric construct containing the extracellular and transmembrane portion of HA spliced to the cytoplasmic portion of the LAMP-1 gene (HA/LAMP).

CLPV:
wherein said chimeric DNA segment is expressed by APC which also express MHC class II molecules and wherein said APC arise from differentiation of said stem cells.

☐ 23. Document ID: US 5587455 A

L6: Entry 23 of 28 File: USPT Dec 24, 1996

DOCUMENT-IDENTIFIER: US 5587455 A
TITLE: Cytotoxic agent against specific virus infection

DEPR:
In evaluating the therapeutic potential of a hybrid toxin, effects on cells other than the desired targets must be considered. Since the natural receptor for CD4 is believed to be the class II major histocompatibility (MHC) molecules on the surface of antigen-presenting cells, B-lymphocytes and macrophages might be affected by the chimeric toxin. Tests indicated, however, that CD4(178)-PE40 did not inhibit protein synthesis in Raji cells, a B-cell line which expresses large amounts of MHC class II molecules. This result is consistent with a published report that soluble CD4 has no inhibitory effect on CD4/MHC class II interactions in vitro, and suggests that monomeric forms of CD4 may have relatively weak affinity for class II antigens.

☐ 24. Document ID: US 5504000 A

L6: Entry 24 of 28 File: USPT Apr 2, 1996

DOCUMENT-IDENTIFIER: US 5504000 A
TITLE: Chimeric protein tyrosine kinases

DEPR:
The CD4 chimeric proteins of the present invention may replace wild-type CD4 as a co-receptor during T cell activation. Association of CD4 extracellular and transmembrane domains with an src tyrosine kinase provides a means to mediate the function of the CD4 cytoplasmic domain in this system. The activity of the chimera required a functional CD4 extracellular domain as the chimeric protein are generally sensitive to mutations in the putative MHC class II binding site of CD4 and may be completely blocked by antibodies against CD4.

DEPR:
Infected cells were sorted to establish a polyclonal cell line expressing the chimeric protein. The same approach was used to prepare cell lines expressing the other constructs described below. The CD4+ cell lines were then tested for their response to stimulation with the antigen, a synthetic peptide analog of hen egg lysozyme, in the presence of antigen-presenting cells expressing the appropriate class II molecule, I-A.sup.b. FIG. 3A illustrates a comparison of responses of T cells expressing no CD4 (the parental 171.3 cells), the CD4/lck chimeric molecule (CtmLck), wild type CD4, mutant CD4 (MCA1) that does not bind p56.sup.lck, and mutant CD4 (MM4) or CD4/lck chimera (CtmLckMM4) that do not bind MHC class II. The T cells were stimulated by co-culturing with the appropriate antigen presenting cells and the peptide antigen at indicated concentrations.

DEPR:
Activated forms of src family kinases can increase IL-2 responses in the absence of a co-receptor interaction with ligand. For example, overexpression of an activated form of Lck has been previously shown to enhance responsiveness of a CD4- T cell hybridoma to stimulation with antigen (Abraham et al., Nature, 350:62-66 (1991). In addition, expression of viral src in another T cell line resulted in constitutive IL-2 expression (O'Shea et al., 1991). In order to rule out the possibility that the mode of action of the CD4/lck chimera was through constitutive activity of the PTK that lowered the threshold for activation, the reported MHC class II binding site of CD4

threshold for activation, the reported MHC class II binding site of CD4 (Lamarre et al., Science, 245:743-746 (1989); Clayton et al., Nature, 339:548-551 (1989), both of which are incorporated herein by reference) was mutated and assayed for functional activity. This mutation completely abolished the function of both CD4 and the CD4/lck chimera (CD4MM4 and CtmLckMM4 in FIG. 3A). The defect in these molecules was confined to the function of the extracellular domain, since antibody-mediated crosslinking of CD3 and the mutant CD4 or CD4/lck chimera resulted in normal levels of tyrosine phosphorylation of cellular substrates and the in vitro kinase activity of the MHC-non-binding mutant chimeric molecule was similar to that of the CtmLck molecule. In addition, the activity of the chimeric molecule in the T cell hybridoma was completely blocked by antibody against CD4 but not by a control MAb against .beta..sub.2 -microglobulin used as a control (FIG. 3B). These results indicate that, like wild type CD4, a functional class II-binding extracellular domain is essential for the activity of the CD4/lck hybrid molecule and confirms that this molecule is appropriately regulated in the 171.3 hybridoma.

☐ 25. Document ID: US 5439819 A

L6: Entry 25 of 28 File: USPT Aug 8, 1995

DOCUMENT-IDENTIFIER: US 5439819 A
TITLE: Chimeric protein tyrosine kinases

DEPR:
The CD4 chimeric proteins of the present invention may replace wild-type CD4 as a co-receptor during T cell activation. Association of CD4 extracellular and transmembrane domains with an src tyrosine kinase provides a means to mediate the function of the CD4 cytoplasmic domain in this system. The activity of the chimera required a functional CD4 extracellular domain as the chimeric protein are generally sensitive to mutations in the putative MHC class II binding site of CD4 and may be completely blocked by antibodies against CD4.

DEPR:
Infected cells were sorted to establish a polyclonal cell line expressing the chimeric protein. The same approach was used to prepare cell lines expressing the other constructs described below. The CD4+cell lines were then tested for their response to stimulation with the antigen, a synthetic peptide analog of hen egg lysozyme, in the presence of antigen-presenting cells expressing the appropriate class II molecule, I-A.sup.b. FIG. 3A illustrates a comparison of responses of T cells expressing no CD4 (the parental 171.3 cells), the CD4/lck chimeric molecule (CtmLck), wild type CD4, mutant CD4 (MCA1) that does not bind p56.sup.lck, and mutant CD4 (MM4) or CD4/lck chimera (CtmLckMM4) that do not bind MHC class II. The T cells were stimulated by co-culturing with the appropriate antigen presenting cells and the peptide antigen at indicated concentrations.

DEPR:
Activated forms of src family kinases can increase IL-2 responses in the absence of a co-receptor interaction with ligand. For example, overexpression of an activated form of Lck has been previously shown to enhance responsiveness of a CD4- T cell hybridoma to stimulation with antigen (Abraham et al., Nature, 350:62-66 (1991). In addition, expression of viral src in another T cell line resulted in constitutive IL-2 expression (O'Shea et al., 1991). In order to rule out the possibility that the mode of action of the CD4/lck chimera was through constitutive activity of the PTK that lowered the threshold for activation, the reported MHC class II binding site of CD4

threshold for activation, the reported MHC class II binding site of CD4 (Lamarre et al., Science, 245:743-746 (1989); Clayton et al., Nature, 339:548-551 (1989), both of which are incorporated herein by reference) was mutated and assayed for functional activity. This mutation completely abolished the function of both CD4 and the CD4/lck chimera (CD4MM4 and CtmLckMM4 in FIG. 3A). The defect in these molecules was confined to the function of the extracellular domain, since antibody-mediated crosslinking of CD3 and the mutant CD4 or CD4/lck chimera resulted in normal levels of tyrosine phosphorylation of cellular substrates and the in vitro kinase activity of the MHC-non-binding mutant chimeric molecule was similar to that of the CtmLck molecule. In addition, the activity of the chimeric molecule in the T cell hybridoma was completely blocked by antibody against CD4 but not by a control MAb against .beta..sub.2 -microglobulin used as a control (FIG. 3B). These results indicate that, like wild type CD4, a functional class II-binding extracellular domain is essential for the activity of the CD4/lck hybrid molecule and confirms that this molecule is appropriately regulated in the 171.3 hybridoma.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 26. Document ID: US 5428143 A

L6: Entry 26 of 28 File: USPT Jun 27, 1995

DOCUMENT-IDENTIFIER: US 5428143 A
TITLE: Cytotoxic agent against specific virus infection

DEPR:
In evaluating the therapeutic potential of a hybrid toxin, effects on cells other than the desired targets must be considered. Since the natural receptor for CD4 is believed to be the class II major histocompatibility (MHC) molecules on the surface of antigen-presenting cells, B-lymphocytes and macrophages might be affected by the chimeric toxin. Tests indicated, however, that CD4(178)-PE40 did not inhibit protein synthesis in Raji cells, a B-cell line which expresses large amounts of MHC class II molecules. This result is consistent with a published report that soluble CD4 has no inhibitory effect on CD4/MHC class II interactions in vitro, and suggests that monomeric forms of CD4 may have relatively weak affinity for class II antigens.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 27. Document ID: US 5328984 A

L6: Entry 27 of 28 File: USPT Jul 12, 1994

DOCUMENT-IDENTIFIER: US 5328984 A
TITLE: Recombinant chimeric proteins deliverable across cellular membranes into cytosol of target cells

DEPR:
The results presented here remarkably show that chimeric proteins containing in part a foreign polypeptide which is normally impermeable to cells, can now be made and delivered to the cytosol in functionally intact form. The polypeptide may, of course, have cytotoxic, therapeutic, diagnostic, or any other desired activity. For example, peptides which usually bind to the cell surface via MHC Class II interactions can be introduced into the cytosol of the presenting cell and given the opportunity to interact with the Class I pathway. Furthermore, if PE were to be used as a translocating vehicle, domain Ia which binds to all cells as a targeting domain, can be replaced with growth factors, antigens, lymphokines, single chain antibodies and the like or with other suitable cell recognition molecules for targeting to specific cells in vitro or in vivo.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 28. Document ID: US 5206353 A

L6: Entry 28 of 28 File: USPT Apr 27, 1993

DOCUMENT-IDENTIFIER: US 5206353 A
TITLE: CD-4/cytotoxic gene fusions

DEPR:
In evaluating the therapeutic potential of a hybrid toxin, effects on cells other than the desired targets must be considered. Since the natural receptor for CD4 is believed to be the class II major histocompatibility (MHC) molecules on the surface of antigen-presenting cells, B-lymphocytes and macrophages might be affected by the chimeric toxin. Tests indicated, however, that CD4(178)-PE40 did not inhibit protein synthesis in Raji cells, a B-cell line which expresses large amounts of MHC class II molecules. This result is consistent with a published report that soluble CD4 has no inhibitory effect on CD4/MHC class II interactions in vitro, and suggests that monomeric forms of CD4 may have relatively weak affinity for class II antigens.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

Generate Collection

Terms	Documents
(MHC ADJ CLASS ADJ II) same (chimeric or hetero$ or dimeri$)	28

Display 28 Documents, starting with Document: 28

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☐ 1. Document ID: US 6232445 B1

L1: Entry 1 of 3 File: USPT May 15, 2001

DOCUMENT-IDENTIFIER: US 6232445 B1
TITLE: Soluble MHC complexes and methods of use thereof

DEPR:
Methods for the immunoaffinity purification of MHC class II molecules have been described previously (Gorga, J. C., V. Horejsi, D. R. Johnson, R. Raghupathy, and J. L. Strominger. (1987) J. Biol. Chem. 262:16087). These methods can be generally employed to purify soluble sc-MHC class I or II proteins of the invention. For example, for sc-MHC class II fusion proteins carrying HLA-DR or HLA-DQ domains, the monoclonal antibodies L243 and G2a.5 (immunospecific for DR and DQ, respectively, and available from ATCC) can be used to immunopurify sc-MHC class II molecules which include these domains. In one example, these methods were employed to purify the sc-DR2.DELTA..beta.2/MBP molecules produced in insect cells (see Example 5). The results of such a purification are shown in FIG. 5B.

CLPR:
1. A sc-MHC class II fusion protein comprising a recombinantly fused polypeptide comprising: i) a presenting peptide and ii) a class II .beta.2 chain comprising at least one amino acid substitution or deletion; wherein the .beta.2 chain increases expression of the fusion protein relative to sc-MHC class II fusion protein comprising the class II .beta.2 chain without the amino acid substitution or deletion.

CLPR:
2. The sc-MHC class II fusion protein of claim 1 further comprising an immunoglobin light chain constant region or fragment thereof.

CLPR:
6. A sc-MHC class II fusion protein comprising a recombinantly fused polypeptide comprising i) a presenting peptide and ii) a immunoglobin light chain constant region or fragment thereof; wherein the immunoglobin light chain constant region or the fragment increases expression of the fusion protein relative to the sc-MHC class II fusion protein without the immunoglobin light chain constant region or fragment.

CLPR:
20. A sc-MHC class II fusion protein comprising covalently linked in sequence:

CLPL:
wherein the increase in expression is relative to sc-MHC class II fusion protein comprising: i) the presenting peptide, ii) the MHC class II .beta.1 chain or presenting-peptide binding portion thereof, iii) the peptide linker

sequence, iv) the MHC class II .alpha.1.alpha.2 chain or a presenting-peptide binding portion thereof, and v) the class II .beta.2 chain without the amino acid substitution or deletion.

CLPL:
wherein the increase in expression is relative to sc-MHC class II fusion protein comprising: i) the presenting peptide, ii) the MHC class II .beta.1 chain or presenting-peptide binding portion thereof, iii) the peptide linker sequence, and iv) the MHC class II .alpha.1.alpha.2 chain or a presenting-peptide binding portion thereof, with the proviso that the sc-MHC class II fusion protein not comprise the immunoglobin light chain constant region or fragment.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

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☐ 2. Document ID: US 6211342 B1

L1: Entry 2 of 3 File: USPT Apr 3, 2001

DOCUMENT-IDENTIFIER: US 6211342 B1
TITLE: Multivalent MHC complex peptide fusion protein complex for stimulating specific T cell function

DEPR:
The fusion protein can be prepared by constructing a gene which encodes for the production of the fusion protein. Alternatively, the components of the fusion protein can be assembled using chemical methods of conjugation. Sources of the genes encoding the MHC molecules and the linkers can be obtained from DNA databases such as GenBank, as well as from published scientific literature in the public domain. In the case of MHC class I fusion proteins, the MHC fragment can be attached to the linker and .beta.2 microglobulin can be allowed to self-associate. Alternatively, the fusion protein gene can be constructed such that .beta.2 microglobulin is attached to the MHC fragment by a ether. In the case of MHC class II fusion protein, either the alpha or the beta chain can be attached to the linker and the other chain can be allowed to self-associate. Alternatively, the fusion protein gene can be constructed such that the alpha and beta chains are connected by a tether. Peptides can be prepared by encoding them into the fusion protein gene construct or, alternatively, with peptide synthesizers using standard methodologies available to one of ordinary skill in the art. The resultant complete fusion proteins can be administered by injection into the patient and can be repeated if necessary to provide a boosting reaction. Generally, the amount of fusion protein administered by injection for therapeutic purposes would range from about 1 .mu.g to about 100 mg per kilogram body weight. With a solid linker, the fusion protein could be injected if microparticles are used, or physically implanted if a larger linker is used.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

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☐ 3. Document ID: US 6197302 B1

L1: Entry 3 of 3 File: USPT Mar 6, 2001

DOCUMENT-IDENTIFIER: US 6197302 B1
TITLE: Method of stimulating T cells

DEPR:
The fusion protein can be prepared by constructing a gene which encodes for the production of the fusion protein. Alternatively, the components of the fusion protein can be assembled using chemical methods of conjugation. Sources of the genes encoding the MHC molecules and the linkers can be obtained from DNA databases such as GenBank, as well as from published scientific literature in the public domain. In the case of MHC class I fusion proteins, the MHC fragment can be attached to the linker and .beta.2 microglobulin can be allowed to self-associate. Alternatively, the fusion protein gene can be constructed such that .beta.2 microglobulin is attached to the MHC fragment by a tether. In the case of MHC class II fusion protein, either the alpha or the beta chain can be attached to the linker and the other chain can be allowed to self-associate. Alternatively, the fusion protein gene can be constructed such that the alpha and beta chains are connected by a tether. Peptides can be prepared by encoding them into the fusion protein gene construct or, alternatively, with peptide synthesizers using standard methodologies available to one of ordinary skill in the art. The resultant complete fusion proteins can be administered by injection into the patient and can be repeated if necessary to provide a boosting reaction. Generally, the amount of fusion protein administered by injection for therapeutic purposes would range from about 1 .mu.g to about 100 mg per kilogram body weight. With a solid linker, the fusion protein could be injected if microparticles are used, or physically implanted if a larger linker is used.

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Dec 17  The CA Lexicon available in the CAPLUS and CA files
 NEWS  3  Feb 06  Engineering Information Encompass files have new names
 NEWS  4  Feb 16  TOXLINE no longer being updated
 NEWS  5  Apr 23  Search Derwent WPINDEX by chemical structure
 NEWS  6  Apr 23  PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS  7  May 07  DGENE Reload
 NEWS  8  Jun 20  Published patent applications (A1) are now in USPATFULL
 NEWS  9  JUL 13  New SDI alert frequency now available in Derwent's
                  DWPI and DPCI

 NEWS EXPRESS  July 11 CURRENT WINDOWS VERSION IS V6.0b,
               CURRENT MACINTOSH VERSION IS V5.0C (ENG) AND V5.0JB (JP),
               AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2001
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=> s (MHC class II) near (fusion or chimeric)
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=> s (MHC class II) (10N) (fusion or chimeric)
L1          185 (MHC CLASS II) (10N) (FUSION OR CHIMERIC)

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2           83 DUP REM L1 (102 DUPLICATES REMOVED)

=> dis l2 1-83 ibib abs kwic

L2   ANSWER 1 OF 83  BIOSIS  COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER:    2001:258569  BIOSIS
DOCUMENT NUMBER:     PREV200100258569
TITLE:               Exploiting the potential to regulate tolerance and immunity
                     through the use of ADP-ribosyltransferase active
                     immunomodulators.
AUTHOR(S):           Wadell, Annemarie Kristina (1); Lycke, Nils (1)
CORPORATE SOURCE:    (1) Institute of laboratory Medicine, Guldhedsgatan 10,
                     Goteborg Sweden
SOURCE:              FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1230.
                     print.
                     Meeting Info.: Annual Meeting of the Federation of American
                     Societies for Experimental Biology on Experimental Biology
                     2001 Orlando, Florida, USA March 31-April 04, 2001
                     ISSN: 0892-6638.
DOCUMENT TYPE:       Conference
LANGUAGE:            English
SUMMARY LANGUAGE:    English
AB   It is probable that mucosal immune responses to soluble protein antigens
     are subject to regulation at the antigen-presenting cell (APC) level,
     implicating that immunomodulation of the APC can promote or prevent active
     immune responses and/or tolerance. We have developed a gene protein,
     CTA1-DD, the targets B cells and effectively delivers antigens to these
     cells. Previous studies have proven that the ADP-ribosyltransferase
     activity of the CTA1-DD adjuvant is critical for the immunoenhancing
     effect of the molecule and that adjuvanticity is associated with
     up-regulation of co-stimulatory molecules on the APC. We constructed novel
     gene fusion proteins with the MHC-class
     II restricted OVA-p323-339 peptide, i.e CTA1-OVA-DD, to enable
     detailed investigations of APC function and CD4 T cell priming in vivo and
     in vitro. Since DD specifically targets B cells via binding to their
     Ig-receptors we asked whether the intact enzymatically active CTA1- or the
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point mutated, enzymatically inactive, CTA[redacted]7K-mutant constructs were efficient enhancers of immune responses to the OVA-peptide. Conversely, the enzymatically inactive mutant was evaluated for its ability to promote tolerance following mucosal exposure. The responses were evaluated after intranasal administration of the constructs and splenic T cell responses were assessed in normal and OVA-peptide specific transgenic T cells as a consequence of exposure to OVA-peptide in the presence or absence of ADP-ribosyltransferase activity. We found that mice immunized with intact CTA1-OVA-DD, but not the enzymatically inactive CTA1-R7K-OVA-DD mutant exhibited enhanced anti-OVA immune responses. By contrast, the enzymatically inactive fusion protein, CTA1-R7K-OVA-DD stimulated tolerance in splenic CD4 T cell populations, supporting our assumption that delivery of antigen to resting B cells in the absence of ADP-ribosylation is an attractive means to induce tolerance in antigen specific T cells.

AB . . . of the molecule and that adjuvanticity is associated with up-regulation of co-stimulatory molecules on the APC. We constructed novel gene **fusion** proteins with the **MHC-class II** restricted OVA-p323-339 peptide, i.e CTA1-OVA-DD, to enable detailed investigations of APC function and CD4 T cell priming in vivo and. . .

L2 ANSWER 2 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:251249 CAPLUS
DOCUMENT NUMBER: 135:32501
TITLE: Regulatory functions of self-restricted MHC class II allopeptide-specific Th2 clones in vivo
AUTHOR(S): Waaga, Ana Maria; Gasser, Martin; Holthe, Joana E. Kist-Van; Najafian, Nader; Muller, Angelika; Vella, John P.; Womer, Karl L.; Chandraker, Anil; Khoury, Samia J.; Sayegh, Mohamed H.
CORPORATE SOURCE: Laboratory of Immunogenetics and Transplantation, Brigham and Women's Hospital, and Children's Hospital, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: J. Clin. Invest. (2001), 107(7), 909-916
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We studied T-cell clones generated from grafts of rejecting and tolerant animals and investigated the regulatory function of Th2 clones in vitro and in vivo. To prevent allograft rejection, we treated LEW strain recipient rats of WF strain kidney grafts with CTLA4Ig to block CD28-B7 costimulation. We then isolated epitope-specific T-cell clones from the engrafted tissue, using a donor-derived immunodominant class II MHC allopeptide presented by recipient antigen-presenting cells. Acutely rejected tissue from untreated animals yielded self-restricted, allopeptide-specific T-cell clones that produced IFN-.gamma., whereas clones from tolerant animals produced IL-4 and IL-10. Adoptive transfer into naive recipients of Th1 clones, but not Th2 clones, induced alloantigen-specific delayed-type hypersensitivity (DTH) responses. In addn., Th2 clones suppressed DTH responses mediated by Th1 clones in vivo and blocked Th1 cell proliferation and IFN-.gamma. prodn. in vitro. A pilot human study showed that HLA-DR allopeptide-specific T-cell clones generated from patients with chronic rejection secrete Th1 cytokines, whereas those from patients with stable graft function produce Th2 cytokines in response to donor-specific HLA-DR allopeptides. We suggest that self-restricted alloantigen-specific Th2 clones may regulate the alloimmune responses and promote long-term allograft survival and tolerance.

REFERENCE COUNT: 39
REFERENCE(S): (1) Azuma, H; Proc Natl Acad Sci USA 1996, V93, P12439 CAPLUS
(2) Chen, W; Transplantation 1996, V62, P705 CAPLUS
(3) Chen, Y; Science 1994, V265, P1237 CAPLUS
(4) Dai, Z; J Immunol 1998, V161, P1659 CAPLUS
(5) Davies, J; J Immunol 1996, V157, P529 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Immunoglobulins
RL: BPR (Biological process); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(G, **fusion** products with CTLA-4 antigen; regulatory functions of self-restricted **MHC class II** allopeptide-specific Th2 clones in vivo and response to)

IT CTLA-4 (antigen)
RL: BPR (Biological process); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(**fusion** products with IgG; regulatory functions of self-restricted **MHC class II** allopeptide-specific Th2 clones in vivo and response to)

L2 ANSWER 3 OF 83 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001324300 MEDLINE
DOCUMENT NUMBER: 21214798 PubMed ID: 11313828
TITLE: MHC class II presentation of endogenously expressed antigens by transfected dendritic cells.
AUTHOR: Diebold S S; Cotten M; Koch N; Zenke M
CORPORATE SOURCE: Max-Delbruck-Center for Molecular Medicine, MDC, Berlin, Germany.
SOURCE: GENE THERAPY, (2001 Mar) 8 (6) 487-93.
Journal code: CCE; 9421525. ISSN: 0969-7128.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607

AB Dendritic cells (DC) present immunogenic epitopes of antigens in the context of MHC class I and class II molecules in association with costimulatory molecules, and efficiently activate both cytotoxic T cells and T helper cells. Gene modified DC expressing antigen encoding cDNA represent a particularly attractive approach for the immunotherapy of disease. We previously described a gene delivery system for DC based on receptor-mediated endocytosis of ligand/polyethylenimine (PEI) DNA transfer complexes that target cell surface receptors which are abundantly expressed on DC. Employing this gene delivery system, DC were generated that express chicken ovalbumin (OVA) cDNA as a model antigen and introduce antigen into the MHC class I presentation pathway. We demonstrate here that modification of OVA cDNA as transferrin receptor (TfR) or invariant chain (Ii) **fusions** effectively generate **MHC class II** specific immune responses in addition to MHC

class I responses. TfR-OVA contains the membrane anchoring region of transferrin receptor and represents a membrane-bound form of OVA for access to the **MHC class II** compartment. Ii-OVA **fusions** directly target the **MHC class** II processing pathway. Thus, modification of antigen encoding cDNA represents a convenient and effective means to direct antigens to MHC class II presentation and thus to generate T cell help.

AB . . . class I presentation pathway. We demonstrate here that modification of OVA cDNA as transferrin receptor (TfR) or invariant chain (Ii) **fusions** effectively generate **MHC class** II specific immune responses in addition to MHC class I responses. TfR-OVA contains the membrane anchoring region of transferrin receptor and represents a membrane-bound form of OVA for access to the **MHC class II** compartment. Ii-OVA **fusions** directly target the **MHC class II** processing pathway. Thus, modification of antigen encoding cDNA represents a convenient and effective means to direct antigens to MHC class. . .

L2 ANSWER 4 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:772470 CAPLUS
DOCUMENT NUMBER: 133:334045
TITLE: Epitope mapping of histone autoepitopes and tolerization of T-cells in systemic lupus erythematosus
INVENTOR(S): Datta, Svamal; Kaliyaperumal, Arunan
PATENT ASSIGNEE(S): Northwestern University, USA
SOURCE: PCT Int. Appl., 135 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000064466	A1	20001102	WO 2000-US11500	20000428

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1999-131448 P 19990428

AB The authors disclose peptides derived from nucleosomal histone proteins which are useful for delaying the onset and progression of systemic lupus erythematosus (i.e. lupus or SLE). The peptides encompass the histones H1, H2A, H2B, H3, and H4. In addn., the authors disclose nucleic acids which encode these histone peptides. In one example, the authors provide the results of epitope mapping of histones using T-cells of lupus patients. In a second example, lupus-prone mice were injected with peptides derived from H2B and H4 histones prior to development of nephropathy. These mice exhibited a delay in nephritis onset and, T-cells isolated from treated animals were reduced in their ability to provide help to autoreactive B-cells. In addn., the authors disclose methods for developing diagnostic and prognostic reagents using the histone peptides and isolated nucleic acids encoding the histone peptides, for the purpose of tracking autoimmune T helper cells and B cells of SLE.

REFERENCE COUNT: 3
REFERENCE(S):
(1) Hafler; US 5645820 A 1997 CAPLUS
(2) Ravirajan; Autoimmunity 1995, V21(2), P117 CAPLUS
(3) Voll; Arthr Rheum 1997, V40(12), P2162 CAPLUS

IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments, **fusion** products, with histone-derived peptides/ **MHC class II**; for immunodiagnosis of systemic lupus erythematosus)

L2 ANSWER 5 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:769010 CAPLUS
DOCUMENT NUMBER: 133:334053
TITLE: Preparation and characterization of sol. multivalent chimeric TCR/Ig or MHC/Ig molecular complexes to analyze and modulate antigen-specific T cell-dependent immune responses
INVENTOR(S): Schneck, Jonathan; O'Herrin, Sean; Lebowitz, Michael S.; Hamad, Abdel
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: U.S., 41 pp., Cont.-in-part of U.S. 6,015,884.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6140113	A	20001031	US 1998-63276	19980421
US 6015884	A	20000118	US 1997-828712	19970328

PRIORITY APPLN. INFO.: US 1996-14367 P 19960328
US 1997-828712 A2 19970328

AB Sol. multivalent chimeric TCR/Ig or MHC/Ig mol. complexes to analyze and modulate antigen-specific T cell-dependent immune responses are described. The mol. complexes comprise extracellular domains of transmembrane heterodimeric proteins, particularly T cell receptor and major histocompatibility complex proteins, which are covalently linked to the heavy and light chains of Ig mols. to provide sol. multivalent mol. complexes with high affinity for their cognate ligands. Studies of the affinity and binding specificity of these multivalent chimeric TCR/Ig or MHC/Ig mols. to antigenic peptides are reported. The mol. complexes can be used, inter alia, to detect and regulate antigen-specific T cells and as therapeutic agents for treating disorders involving immune system regulation, such as allergies, autoimmune diseases, tumors, infections, and transplant rejection.

REFERENCE COUNT: 11
REFERENCE(S):
(1) Anon; WO 9310220 1993 CAPLUS
(2) Anon; WO 9604314 1996 CAPLUS
(3) Chang, H; Proceedings of the National Academy of Sciences of the USA 1994, V91, P11408 CAPLUS
(4) Dal Porto, J; Proceedings of the National Academy of Science of the USA 1993, V90(14), P6671 CAPLUS
(5) Eilat, D; Proceedings of the National Academy of Sciences of the USA 1992, V89(15), P6871 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ST TCR receptor Ig fusion protein immune response modulation; **MHC class II** Ig **fusion** protein immune response modulation

L2 ANSWER 6 OF 83 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001086806 MEDLINE
DOCUMENT NUMBER: 20558264 PubMed ID: 11106438
TITLE: Expression and characterization of truncated forms of humanized L243 IgG1. Architectural features can influence synthesis of its oligosaccharide chains and affect superoxide production triggered through human Fcgamma receptor I.
AUTHOR: Lund J; Takahashi N; Popplewell A; Goodall M; Pound J D; Tyler R; King D J; Jefferis R
CORPORATE SOURCE: Department of Immunology, The Medical School, Birmingham, UK.. J.Lund@bham.ac.uk
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (2000 Dec) 267 (24) 7246-57.
Journal code: EMZ. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

AB The properties of IgG and its subcomponents are being exploited to generate new therapeutics with selected biological activities. In this study, a series of truncated, humanized IgG1 antibodies was expressed in Chinese hamster ovary cells, to evaluate the contribution of structural components to glycosylation and function. The series includes L243 IgG1 (alpha-**MHC Class II**) lacking a CH3 domain pair (DeltaCH3-IgG1), single-chain Fv **fusion** proteins with Fc or a hinge-CH2 domain, Fc with/out a hinge, and a single CH2 domain. Glycosylation of IgG Fc is important for recognition by effector ligands such as Fcgamma receptors. HPLC analysis of released and pyridylaminated oligosaccharides indicates that intact IgG1 and scFvFc antibodies are galactosylated and sialylated to levels similar to those observed previously for normal human IgG1. The truncated forms express increased levels of digalactosylated (30-83%) or sialylated (9-21%) oligosaccharide chains with the highest levels observed for the single CH2 domain. These data show which architectural components influence IgG glycosylation processing and that the (CH3)2 pair is particularly influential. When MHC Class II bearing (JY) cells were sensitized with L243 DeltaCH3-IgG1, scFvFc, or scFvhCH2 they elicited superoxide production, from U937 cells, at levels of 35-45% relative to that obtained for intact L243 IgG1 (100%). Mild reduction and alkylation of the hinge disulphide bonds of scFvhCH2 greatly decreased its capacity to trigger superoxide production. Thus, the L243 scFvhCH2 homo-dimer constitutes the minimal truncated form that binds the MHC Class II antigen and triggers superoxide production through FcgammaRI.

AB . . . Chinese hamster ovary cells, to evaluate the contribution of structural components to glycosylation and function. The series includes L243 IgG1 (alpha-**MHC Class II**) lacking a CH3 domain pair (DeltaCH3-IgG1), single-chain Fv **fusion** proteins with Fc or a hinge-CH2 domain, Fc with/out a hinge, and a single CH2 domain. Glycosylation of IgG Fc. . .

L2 ANSWER 7 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:217911 CAPLUS
DOCUMENT NUMBER: 133:3474
TITLE: Identification of a MHC class II-restricted human gp100 epitope using DR4-IE transgenic mice
AUTHOR(S): Touloukian, Christopher E.; Leitner, Wolfgang W.; Topalian, Suzanne L.; Li, Yong F.; Robbins, Paul F.; Rosenberg, Steven A.; Restifo, Nicholas P.
CORPORATE SOURCE: Surgery Branch, National Cancer Institute, Bethesda, MD, 20892, USA
SOURCE: J. Immunol. (2000), 164(7), 3535-3542
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CD4+ T cells play a central role in the induction and persistence of CD8+ T cells in several models of autoimmune and infectious disease. To improve the efficacy of a synthetic peptide vaccine based on the self-Ag, gp100, we sought to provide Ag-specific T cell help. To identify a gp100 epitope restricted by the MHC class II allele with the highest prevalence in patients with malignant melanoma (HLA-DRB1*0401), we immunized mice transgenic for a chimeric human-mouse class II mol. (DR4-IE) with recombinant human gp100 protein. We then searched for the induction of CD4+ T cell reactivity using candidate epitopes predicted to bind to DRB1*0401 by a computer-assisted algorithm. Of the 21 peptides forecasted to bind most avidly, murine CD4+ T cells recognized the epitope (human gp10044-59, WNRQLYPEWTEAQRLD) that was predicted to bind best. Interestingly, the mouse helper T cells also recognized human melanoma cells expressing DRB1*0401. To evaluate whether human CD4+ T cells could be generated from the peripheral blood of patients with melanoma, we used the synthetic peptide h-gp10044-59 to sensitize lymphocytes ex vivo. Resultant human CD4+ T cells specifically recognized melanoma, as measured by tumor cytolysis and the specific release of cytokines and chemokines. HLA class II transgenic mice may be useful in the identification of helper epitopes derived from Ags of potentially great clin. utility.

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(4) Cardin, R; J Exp Med 1996, V184, P863 CAPLUS
(5) Chaux, P; J Exp Med 1999, V189, P767 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **Chimeric** gene
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); MFM (Metabolic formation); PRP (Properties); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(identification of a **MHC class II**
-restricted human gp100 epitope using DR4-IE transgenic mice)

L2 ANSWER 8 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:359370 CAPLUS
DOCUMENT NUMBER: 133:118842
TITLE: Cooperativity of Staphylococcal aureus enterotoxin B superantigen, major histocompatibility complex class II, and CD80 for immunotherapy of advanced spontaneous metastases in a clinically relevant postoperative

mouse breast cancer m

AUTHOR(S): Pulaski, Beth A.; Terman, David S.; Khan, Saleem; Muller, Eric; Ostrand-Rosenberg, Suzanne

CORPORATE SOURCE: Department of Biological Sciences, University of Maryland Baltimore County, Baltimore, MD, 21250, USA

SOURCE: Cancer Res. (2000), 60(10), 2710-2715
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal.

LANGUAGE: English

AB One of the leading causes of death for women is metastatic breast cancer. Because most animal tumors do not accurately model clin. metastatic disease, the development of effective therapies has progressed slowly. In this study, we establish the poorly immunogenic mouse 4T1 mammary carcinoma as a postsurgical animal model. The 4T1 growth characteristics parallel highly invasive human metastatic mammary carcinoma and, at the time of surgery, the extent of disease is comparable with human stage IV breast cancer. Progress in understanding the immune response has led to innovative immune-based anticancer therapies. Here, we test in this postsurgical model, a novel cell-based vaccine, combining MHC class II, CD80 (B7.1), and SEB superantigen. Effective treatment of tumor-bearing mice with this immunotherapy requires expression of all three mols. Mean survival time is extended from 5-7.5 wk for control-treated mice to 6-10.5 wk for therapy-treated mice. Increased survival is accompanied by a max. of 100-fold decrease in clonogenic lung metastases. These therapeutic effects are particularly noteworthy because: (a) the postoperative model demonstrates that early metastases responsible for morbidity are established by 2 wk after tumor inoculation with 7 .times. 103 parental 4T1 cells into the mammary gland; (b) the immunotherapy is started 4 wk after tumor inoculation when the mice contain extensive, pre-established, disseminated metastases; and (c) CD4+ and CD8+ T cells are required for the effect.

REFERENCE COUNT: 36

REFERENCE(S): (1) Armstrong, T; J Immunol 1998, V160, P661 CAPLUS
(4) Baskar, S; J Exp Med 1995, V181, P619 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **Chimeric** gene
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(cooperativity of Staphylococcal aureus enterotoxin B, MHC **class II**, and CD80 for immunotherapy of advanced spontaneous metastases in clin. relevant postoperative mouse breast cancer model)

L2 ANSWER 9 OF 83 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:450262 CAPLUS

DOCUMENT NUMBER: 134:84797

TITLE: Increasing the potency of MHC class II-presented epitopes by linkage to Ii-Key peptide

AUTHOR(S): Humphreys, R. E.; Adams, S.; Koldzic, G.; Nedelescu, B.; Von Hofe, E.; Xu, M.

CORPORATE SOURCE: Antigen Express Inc, Worcester, MA, 01605-4306, USA

SOURCE: Vaccine (2000), 18(24), 2693-2697
CODEN: VACCDE; ISSN: 0264-410X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We previously found that peptide Ii77-92 from the immunoregulatory Ii protein significantly enhances the binding of antigenic peptides to MHC class II mols. Now a series of hybrids have been constructed linking LRMK, the active core region of the Ii77-92 peptide, to an antigenic epitope of cytochrome C. In vitro T cell hybridoma stimulation by some of these hybrids is up to 250 times more potent than by the antigenic peptide. The biol. activities of the hybrids were tested in terms of length and compn. of the linker. Simple spacers contg. a polymethylene bridge (-HN-CH2-CH2-CH2-CH2-CO2-) were fully active in these hybrids which can enhance vaccination with MHC class II-presented epitopes.

REFERENCE COUNT: 16

REFERENCE(S): (1) Adams, S; Arznei-Forsch 1997, V47, P1069 CAPLUS
(3) Adams, S; Eur J Immun 1995, V25, P1693 CAPLUS
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(6) Daibata, M; Mol Immun 1994, V31, P255 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Peptides, biological studies
RL: BPR (Biological process); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(**fusion** peptides; increasing the potency of **MHC class II**-presented epitopes by linkage to Ii-Key peptide)

L2 ANSWER 10 OF 83 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:593498 CAPLUS

DOCUMENT NUMBER: 133:280255

TITLE: Characterization of MHC class II-presented peptides generated from an antigen targeted to different endocytic compartments

AUTHOR(S): Fernandes, Dancella M.; Vidard, Laurent; Rock, Kenneth L.

CORPORATE SOURCE: Department of Pathology, University of Massachusetts Medical Center, Worcester, MA, USA

SOURCE: Eur. J. Immunol. (2000), 30(8), 2333-2343
CODEN: EJIMAF; ISSN: 0014-2980

PUBLISHER: Wiley-VCH Verlag GmbH

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors evaluated the capacity of the secretory pathway or of different endocytic compartments in B cell lines to generate MHC class II-presented peptides from the antigen ovalbumin (OVA). Sorting signals from the transferrin receptor (TFR), targeted a chimeric OVA fusion protein to early endosomes and led to the generation of 8 of 12 presented peptides. Sorting signals from the lysosome-assocd. membrane protein 1 (LAMP-1), targeted an OVA fusion protein to lysosomes, and led to the generation of 9 of 12 peptides. In contrast, OVA with only a signal sequence led to the generation of only 2 presented peptides. There were both qual. and quant. differences in the generation of peptides from the different fusion proteins, suggesting that multiple distinct compartments

are involved in generating different epitop[redacted] One peptide was presented better from the TFR fusion protein, while all others were presented better from the LAMP-1 construct. Twelve peptides were generated from exogenously supplied OVA, including 3 peptides that were not generated from any of the fusion proteins. Since most endogenously synthesized foreign antigens are rarely presented on class II mols., these studies further suggest a strategy whereby antigens in DNA-based vaccines could be targeted to endocytic compartments to enhance immunogenicity.

REFERENCE COUNT: 54
REFERENCE(S):
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(4) Barnes, K; J Exp Med 1995, V181, P1715 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **Fusion** proteins (**chimeric** proteins)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(processing and **MHC class II** presentation of model antigen fused to endosomal sorting signals)

L2 ANSWER 11 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:355305 CAPLUS
DOCUMENT NUMBER: 134:16333
TITLE: Recombinant expression and neutralizing activity of an MHC class II binding epitope of toxic shock syndrome toxin-1
AUTHOR(S): Rubinchik, Evelina; Chow, Anthony W.
CORPORATE SOURCE: Division of Infectious Diseases, Department of Medicine, Canadian Bacterial Disease Network, University of British Columbia, Vancouver, BC, V5Z 3J5, Can.
SOURCE: Vaccine (2000), 18(21), 2312-2320
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Toxic shock syndrome (TSS) is caused by the staphylococcal superantigen, TSST-1. The MHC class II binding domain of TSST-1 contg. a conserved sequence with other related staphylococcal enterotoxins, comprising TSST-1 residues 47-64 [T(47-64)], was expressed as a fusion protein with either glutathione-S-transferase (GST47-64), filamentous phage coat protein (pIII47-64), or E. coli outer membrane porin protein (OprF47-64), or synthesized as a peptide conjugated to bovine serum albumin, BSA47-64. GST47-64, OprF47-64 and BSA47-64, but not pIII47-64, all induced high-titer T(47-64)-specific antibodies in Balb/c mice. However, only anti-GST47-64 antibodies inhibited 125I-TSST-1 binding to MHC class II and abrogated TSST-1-induced T cell mitogenesis and TNF.alpha. secretion in human peripheral blood mononuclear cells. Purified GST47-64 also inhibited 125I-TSST-1 binding in a dose-dependent manner. These findings suggest that GST47-64 may have potential as a recombinant peptide vaccine or TSST-1 receptor inhibitor against TSS.

REFERENCE COUNT: 36
REFERENCE(S):
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(5) Donnelly, R; Cell Immun 1982, V72, P166 CAPLUS
(6) Finnen, R; J Bacteriol 1992, V174, P4977 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **Fusion** proteins (**chimeric** proteins)
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(GST-TSST-1 epitope; neutralizing activity of **MHC class II** binding epitope of staphylococcal toxic shock syndrome toxin-1)

L2 ANSWER 12 OF 83 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000214142 MEDLINE
DOCUMENT NUMBER: 20214142 PubMed ID: 10752477
TITLE: Phage-selected primate antibodies fused to superantigens for immunotherapy of malignant melanoma.
AUTHOR: Tordsson J M; Ohlsson L G; Abrahmsen L B; Karlstrom P J; Lando P A; Brodin T N
CORPORATE SOURCE: Active Biotech Research AB, Lund, Sweden..
Jesper.Tordsson@activebiotech.com
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (2000 Mar) 48 (12) 691-702.
Journal code: CN3; 8605732. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000427
Last Updated on STN: 20000427
Entered Medline: 20000419

AB The high-molecular-weight melanoma-associated antigen, HMW-MAA, has been demonstrated to be of potential interest for diagnosis and treatment of malignant melanoma. Murine monoclonal antibodies (mAb) generated in response to different epitopes of this cell-surface molecule efficiently localise to metastatic lesions in patients with disseminated disease. In this work, phage-display-driven selection for melanoma-reactive antibodies generated HMW-MAA specificities capable of targeting bacterial superantigens (SAg) and cytotoxic T cells to melanoma cells. Cynomolgus monkeys were immunised with a crude suspension of metastatic melanoma. A strong serological response towards HMW-MAA demonstrated its role as an immunodominant molecule in the primate. Several clones producing monoclonal scFv antibody fragments that react with HMW-MAA were identified using melanoma cells and tissue sections for phage selection of a recombinant antibody phage library generated from lymph node mRNA. One of these scFv fragments, K305, was transferred and expressed as a Fab-SAg fusion protein and evaluated as the tumour-targeting moiety for superantigen-based immunotherapy. It binds with high affinity to a unique human-specific epitope on the HMW-MAA, and demonstrates more restricted cross-reactivity with normal smooth-muscle cells than previously described murine mAb. The K305 Fab was fused to the superantigen staphylococcal enterotoxin A (D227A) [SEA(D227A)], which had been mutated to reduce its intrinsic **MHC class II** binding affinity, and the **fusion** protein was used to demonstrate redirection of T cell cytotoxicity to melanoma cells in vitro. In mice with severe combined immunodeficiency, carrying human melanoma tumours, engraftment of human lymphoid cells followed by treatment with the K305Fab-SEA(D227A) fusion

protein, induced HMW-MAA-specific tumour g[illegible]n reduction. The phage-selected K305 antibody demonstrated high-affinity binding and selectivity, supporting its use for tumour therapy in conjunction with T-cell-activating superantigens.

AB . . . K305 Fab was fused to the superantigen staphylococcal enterotoxin A (D227A) [SEA(D227A)], which had been mutated to reduce its intrinsic **MHC class II** binding affinity, and the **fusion** protein was used to demonstrate redirection of T cell cytotoxicity to melanoma cells in vitro. In mice with severe combined. .

L2 ANSWER 13 OF 83 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000164583 MEDLINE
DOCUMENT NUMBER: 20164583 PubMed ID: 10699939
TITLE: Hybrid cell vaccination for cancer immune therapy: first clinical trial with metastatic melanoma.
AUTHOR: Trefzer U; Weingart G; Chen Y; Herberth G; Adrian K; Winter H; Audring H; Guo Y; Sterry W; Walden P
CORPORATE SOURCE: Department of Dermatology, Medical Faculty Charite, Humboldt University, Berlin, Germany.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (2000 Mar 1) 85 (5) 618-26.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000322

AB Hybrid cell vaccination is a new cancer immune therapy approach that aims at recruiting T cell help for the induction of tumour specific cytolytic immunity. The vaccines are generated by **fusion** of the patients' tumour cells with allogeneic **MHC class II** bearing cells to combine the tumour's antigenicity with the immunogenicity of allogeneic MHC molecules. Safety and anti-tumour activity of this treatment were assessed in a clinical trial that has yielded one complete and one partial remission, and 5 cases of stable disease among 16 patients with advanced stage metastatic melanoma. As evidenced by histology, the vaccination induced T cell relocation into tumour nodules. Stable disease could be maintained by repeated booster injections for more than 24 months in some patients. The side effects were minor. Occasional occurrences of vitiligo spots after vaccination were indicative of a restricted therapy induced auto-immune reactivity. The results suggest that hybrid cell vaccination is a safe cancer immune therapy potentially effective for induction of acute anti-tumour response as well as long-term maintenance. Copyright 2000 Wiley-Liss, Inc.

AB . . . that aims at recruiting T cell help for the induction of tumour specific cytolytic immunity. The vaccines are generated by **fusion** of the patients' tumour cells with allogeneic **MHC class II** bearing cells to combine the tumour's antigenicity with the immunogenicity of allogeneic MHC molecules. Safety and anti-tumour activity of this. . .

L2 ANSWER 14 OF 83 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001322256 MEDLINE
DOCUMENT NUMBER: 21129043 PubMed ID: 11208113
TITLE: Pathways for lipid antigen presentation by CD1 molecules: nowhere for intracellular pathogens to hide.
AUTHOR: Sugita M; Peters P J; Brenner M B
CORPORATE SOURCE: Lymphocyte Biology Section, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.
SOURCE: TRAFFIC, (2000 Apr) 1 (4) 295-300. Ref: 54
Journal code: DX7; 100939340. ISSN: 1398-9219.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607

AB A crucial feature of peptide antigen presentation by major histocompatibility complex (MHC) class I and II molecules is their differential ability to sample cytosolic and extracellular antigens. Intracellular viral infections and bacteria that are taken up in phagosomes, but then escape from the endocytic compartment efficiently, enter the class I pathway via the cytosol. In contrast, phagosome-resident bacteria yield protein antigens that are sampled deep in the endocytic compartment and presented in a vacuolar acidification-dependent pathway mediated by MHC class II molecules. Despite this potential for antigen sampling, microbes have evolved a variety of evasive mechanisms that affect peptide transport in the MHC class I pathway or blockade of endosomal acidification and inhibition of phagosome-lysosome **fusion** that may compromise the **MHC class II** pathway of antigen presentation. Thus, besides MHC class I and II, a third lineage of antigen-presenting molecules that bind lipid and glycolipid antigens rather than peptides exists and is mediated by the family of CD1 proteins. CD1 isoforms (CD1a, b, c, and d) differentially sample both recycling endosomes of the early endocytic system and late endosomes and lysosomes to which lipid antigens are differentially delivered. These CD1 pathways include vacuolar acidification-independent pathways for lipid antigen presentation. These features of presenting lipid antigens, independently monitoring various antigen-containing intracellular compartments and avoiding certain evasive techniques employed by microbes, enable CD1 molecules to provide distinct opportunities to function in host defense against the microbial world.

AB . . . mechanisms that affect peptide transport in the MHC class I pathway or blockade of endosomal acidification and inhibition of phagosome-lysosome **fusion** that may compromise the **MHC class II** pathway of antigen presentation. Thus, besides MHC class I and II, a third lineage of antigen-presenting molecules that bind lipid. . .

L2 ANSWER 15 OF 83 MEDLINE DUPLICATE 6

ACCESSION NUMBER: 2000130132 MEDLINE
DOCUMENT NUMBER: 20130132 PubMed ID: 10663561
TITLE: Defective MHC class II expression in an MHC class II deficiency patient is caused by a novel deletion of a splice donor site in the MHC class II transactivator gene.
AUTHOR: Peijnenburg A; Van den Berg R; Van Eggermond M J; Sanal O; Vossen J M; Lennon A M; Alcaide-Loridan C; Van den Elsen P J
CORPORATE SOURCE: Department of Immunohematology and Blood Bank, Leiden University Medical Center, Building 1, E3-Q, P.O. Box 9600, 2300 RC Leiden, The Netherlands.
SOURCE: IMMUNOGENETICS, (2000 Jan) 51 (1) 42-9.
Journal code: GI4; 0420404. ISSN: 0093-7711.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000229

AB MHC class II deficiency patients are mutated for transcription factors that regulate the expression of major histocompatibility complex (MHC) class II genes. Four complementation groups (A-D) are defined and the gene defective in group A has been shown to encode the MHC class II transactivator (CIITA). Here, we report the molecular characterization of a new **MHC class II** deficiency patient, ATU.
Cell **fusion** experiments indicated that ATU belongs to complementation group A. Subsequent mutation analysis revealed that the CIITA mRNA lacked 84 nucleotides. This deletion was the result of the absence of a splice donor site in the CIITA gene of ATU. As a result of this novel homozygous genomic deletion, ATU CIITA failed to transactivate MHC class II genes. Furthermore, this truncated CIITA of ATU did not display a dominant negative effect on CIITA-mediated transactivation of various isotypic MHC class II promoters.

AB . . . has been shown to encode the MHC class II transactivator (CIITA). Here, we report the molecular characterization of a new **MHC class II** deficiency patient, ATU. Cell **fusion** experiments indicated that ATU belongs to complementation group A. Subsequent mutation analysis revealed that the CIITA mRNA lacked 84 nucleotides.. . .

L2 ANSWER 16 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:123096 CAPLUS
DOCUMENT NUMBER: 133:139861
TITLE: Tumorigenicity and immunogenicity of murine tumor cells expressing an MHC class II molecule with a covalently bound antigenic peptide
AUTHOR(S): Ladanyi, Andrea; Nishimura, Michael I.; Rosenberg, Steven A.; Yang, James C.
CORPORATE SOURCE: Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: J. Immunother. (2000), 23(1), 36-47
CODEN: JOIMF8; ISSN: 1053-8550
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The significance of CD4+ lymphocytes and major histocompatibility complex (MHC) class II-restricted antigens in antitumor immunity has been demonstrated in several animal models as well as in some human tumors. However, because of the lack of known class II-restricted antigens, the participation of CD4+ cells in antitumor responses has not been well characterized. Recent reports showed that class II proteins covalently linked to an antigenic peptide could be constructed and cells expressing these fusion proteins were recognized by specific TH cells. The aim of this study was to det. the effect of the expression of a class II-peptide construct on the tumorigenicity and immunogenicity of transfected murine tumor cells. We have constructed a gene for I-Ed .beta. chain covalently coupled to the I-Ed-restricted TH cell determinant of sperm whale myoglobin (SWM132-145). This class II fusion protein was recognized by a specific TH cell line on the surface of COS-7 cells or BALB/c sarcoma cells. The sarcoma cells expressing the MHC-peptide complex were rejected by immunocompetent BALB/c mice, and in vivo T-cell subset depletion expts. suggested the importance of CD4+ cells in the rejection. Moreover, splenocytes from mice immunized with tumor cells expressing the I-Ed-SWM complex showed specific peptide recognition in vitro. Such covalent MHC-peptide complexes could prove useful in studies on the role of CD4+ lymphocytes in antitumor immune responses, and also in designing new, more effective vaccine approaches to the immunotherapy of cancer, as class II-restricted tumor-assocd. antigens are identified for human cancers.

REFERENCE COUNT: 43
REFERENCE(S): (1) Baskar, S; Cell Immunol 1994, V155, P123 CAPLUS
(2) Baskar, S; J Exp Med 1995, V181, P619 CAPLUS
(3) Baskar, S; Proc Natl Acad Sci USA 1993, V90, P5687 CAPLUS
(4) Berkower, I; J Immunol 1985, V135, P2628 CAPLUS
(5) Bloom, M; J Exp Med 1997, V185, P453 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Fusion proteins (**chimeric** proteins)
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumorigenicity and immunogenicity of murine tumor cells expressing **MHC class II** mol. with a covalently bound antigenic peptide)

L2 ANSWER 17 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:549393 CAPLUS
DOCUMENT NUMBER: 131:183867
TITLE: Monovalent, multivalent, and multimeric MHC binding domain fusion proteins and conjugates, and uses therefor
INVENTOR(S): Wucherpfennig, Kai W.; Strominger, Jack L.
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942597	A1	19990826	WO 1999-US3603	19990219

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9927748	A1	19990906	AU 1999-27748	19990219
BR 9908082	A	20001031	BR 1999-8082	19990219
EP 1054984	A1	20001129	EP 1999-908272	19990219

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1998-75351 P 19980219
WO 1999-US3603 W 19990219

AB The present invention is directed to the design, prodn., and use of monovalent, multivalent and multimeric major histocompatibility complex binding domain fusion proteins and conjugates. The MHC **fusion** proteins and conjugates may comprise **MHC class** II .alpha. or .beta. chain (HLA-DRA*0101, HLA-DRA*0102, HLA-DQA1*0301, HLA-DRB1*01, etc.), leucine zipper domain of Fos or Jun, linker peptide, yeast .sigma.-mating factor secretion signal, human myelin basic protein tag, IgG or IgE or IgM Fc, and optionally cytotoxic substance (human desmoglein 3 protein peptide). The MHC binding domain fusion proteins and conjugates are useful for diagnosis and treatment of diseases assocd. with T cell-mediated immune response and antigen presentation, e.g. autoimmune disease, multiple sclerosis and rheumatoid arthritis. Thus, fusion proteins contg. HLA-DR2 .alpha. chain (.beta. chain), Fos (Jun) leucine zipper dimerization domain, VDGGGGG linker, and .alpha.-mating secretion signal were prepd., fused with IgG2a or IgM, tagged with MBP peptide, conjugated with bead carrier, and used for selectively depletion of T cells.

REFERENCE COUNT: 8
REFERENCE(S):
(1) Casares, S; WO 9909064 A 1999 CAPLUS
(2) Children's Hospital Medical Center; WO 9803552 A 1998 CAPLUS
(4) Kalandadze, A; Journal of Biological Chemistry 1996, V271(33), P20156 CAPLUS
(5) Nag, B; Journal of Biological Chemistry 1996, V271(17), P10413 CAPLUS
(6) Schneck, J; WO 9735991 A 1997 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The present invention is directed to the design, prodn., and use of monovalent, multivalent and multimeric major histocompatibility complex binding domain fusion proteins and conjugates. The MHC **fusion** proteins and conjugates may comprise **MHC class** II .alpha. or .beta. chain (HLA-DRA*0101, HLA-DRA*0102, HLA-DQA1*0301, HLA-DRB1*01, etc.), leucine zipper domain of Fos or Jun, linker peptide, yeast .sigma.-mating factor secretion signal, human myelin basic protein tag, IgG or IgE or IgM Fc, and optionally cytotoxic substance (human desmoglein 3 protein peptide). The MHC binding domain fusion proteins and conjugates are useful for diagnosis and treatment of diseases assocd. with T cell-mediated immune response and antigen presentation, e.g. autoimmune disease, multiple sclerosis and rheumatoid arthritis. Thus, fusion proteins contg. HLA-DR2 .alpha. chain (.beta. chain), Fos (Jun) leucine zipper dimerization domain, VDGGGGG linker, and .alpha.-mating secretion signal were prepd., fused with IgG2a or IgM, tagged with MBP peptide, conjugated with bead carrier, and used for selectively depletion of T cells.

L2 ANSWER 18 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:297317 CAPLUS
DOCUMENT NUMBER: 130:295539
TITLE: Construction of chimeric soluble MHC complexes
INVENTOR(S): Rhode, Peter R.; Acevedo, Jorge; Burkhardt, Martin; Jiao, Jin-an; Wong, Hing C.
PATENT ASSIGNEE(S): Sunol Molecular Corporation, USA
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9921572	A1	19990506	WO 1998-US21520	19981013

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6232445	B1	20010515	US 1997-960190	19971029
AU 9898001	A1	19990517	AU 1998-98001	19981013
EP 1027066	A1	20000816	EP 1998-952256	19981013

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1997-960190 A 19971029
WO 1998-US21520 W 19981013

AB The authors disclose the construction and expression of sol. single-chain (s.c.) MHC class II mols. In one aspect, the s.c.-MHC class II mols. include a .beta.2 chain modification, e.g., deletion of essentially the entire class II .beta.2 domain. In another aspect, the invention features single-chain MHC class II which contain an Ig light chain const. region fragment (CL). The CL fragment allows multimerization of single-chain monomers of identical or disparate MHC specificity or formation of heteromeric mols. with effector function (e.g., single-chain antibodies). In addn., the sol. MHC class II mols. can be constructed for exogenous loading of cognate peptides or the requisite peptides can be included in the single-chain constructs themselves. In one example, single-chain I-Ad mols. were constructed as fusion proteins with T-cell epitopes from either ovalbumin or glycoprotein D of herpes simplex virus. These constructs were shown to stimulate interleukin-2 prodn. by their resp. antigen-specific T-cells. MHC complexes of the invention are useful for a variety of applications including: (1) in vitro screens for identification and isolation of peptides that modulate activity of selected T-cells, including peptides that are T cell receptor antagonists and partial agonists, and (2) methods for suppressing or inducing an immune response in a mammal.

REFERENCE COUNT: 4

REFERENCE(S): (1) Gorga, J; Crit Re[redacted]munol 1992, V11(5), P305 CAPLUS
(2) Marguiles, D; Immunol Res 1987, V6, P101
(3) Nag, B; P N A S 1993, V90, P1604 CAPLUS
(4) Sharma; US 5130297 A 1992 CAPLUS

ST soluble histocompatibility class II antigen fusion protein; single chain **MHC class II** soluble **fusion** protein

IT Immunoglobulin fragments
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(CL, **fusion** products with single-chain **MHC class II** mols.; prepn., enhanced soly., and biol. activity of)

IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(**fusion** peptides, with single-chain **MHC class II** mols.; prepn. and biol. activity of)

IT Immunoglobulin light chains
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(**fusion** products, with single-chain **MHC class II** mols.; prepn., enhanced soly., and biol. activity of)

IT **Fusion** proteins (**chimeric** proteins)
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(of sol. single-chain **MHC class II** heterodimers with, or without, **fusion** to T-cell epitopes and/or Ig light chain const. region fragments)

L2 ANSWER 19 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:139879 CAPLUS
DOCUMENT NUMBER: 130:208806
TITLE: Epitope-bearing major histocompatibility complex class II element/immunoglobulin chimeric molecules
INVENTOR(S): Casares, Sofia; Brumeanu, Teodor Doru; Bona, Constantin
PATENT ASSIGNEE(S): Mount Sinai School of Medicine of the City of New York, USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9909064	A1	19990225	WO 1997-US20023	19971104
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9854285	A1	19990308	AU 1998-54285	19971104
EP 1007567	A1	20000614	EP 1997-948162	19971104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-56185 P 19970819
WO 1997-US20023 W 19971104

AB The present invention describes the construction of immunol. active mols. comprising (1) a **fusion** protein contg. a peptide epitope, an extracellular domain of an **MHC class II** subunit, and the Fc domain of IgG2a and (2) a **fusion** protein of the complementary **MHC class II** subunit extracellular domain and the Fc domain of IgG2a. These fusion proteins are covalently joined by one or more disulfide linkages present in the Ig const. region element. The resulting heterodimeric mols. were shown to eliminate T cells bearing antigen receptors which recognize the epitope of interest in the context of the MHC class II element. Therefore, they may be used to eliminate or reduce specific T cell populations, for example, in the treatment of autoimmune and/or graft-vs. host diseases.

REFERENCE COUNT: 4
REFERENCE(S): (1) Maddon; US 5126433 1992 CAPLUS
(2) Margulies, D; Immunol Res 1987, V6, P101 CAPLUS
(3) Reinherz; US 5109123 A 1992 CAPLUS
(4) Sharma; US 5130297 A 1992 CAPLUS

AB The present invention describes the construction of immunol. active mols. comprising (1) a **fusion** protein contg. a peptide epitope, an extracellular domain of an **MHC class II** subunit, and the Fc domain of IgG2a and (2) a **fusion** protein of the complementary **MHC class II** subunit extracellular domain and the Fc domain of IgG2a. These fusion proteins are covalently joined by one or more disulfide linkages present in the Ig const. region element. The resulting heterodimeric mols. were shown to eliminate T cells bearing antigen receptors which recognize the epitope of interest in the context of the MHC class II element. Therefore, they may be used to eliminate or reduce specific T cell populations, for example, in the treatment of autoimmune and/or graft-vs. host diseases.

ST epitope **fusion MHC class II** chimera Ig; T cell lysis **MHC class II** **fusion** protein

IT Immunoglobulin heavy chains
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); PRP (Properties); BIOL (Biological study); PREP (Preparation); PROC (Process)
(Fc fragment, **fusion** product with **MHC class II** and peptide epitope; prepn. and T-cell cytolytic activity of)

IT Complement activation
(by heterodimeric **fusion** proteins of **MHC class II** extracellular domains and Ig Fc.gamma.2a fragments and contg. peptide epitope)

IT Cytolysis
(complement-dependent; of T-cells by heterodimeric **fusion** proteins of **MHC class II** extracellular domains and Ig Fc.gamma.2a fragments and contg. peptide epitope)

IT CD4-positive T cell
(cytolysis of T-cells by heterodimeric **fusion** proteins of **MHC class II** extracellular domains and Ig Fc.gamma.2a fragments and contg. TCR-relevant peptide epitope)

IT TCR (T cell receptors)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cytolysis of T-cells by heterodimeric **fusion** proteins of **MHC class II** extracellular domains and Ig Fc.gamma.2a fragments and contg. peptide epitope recognized by)
IT Disulfide bond
(for covalent assocn. of heterodimeric **fusion** proteins of **MHC class II** extracellular domains and Ig Fc.gamma.2a fragments and contg. peptide epitope)
IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); PRP (Properties); BIOL (Biological study); PREP (Preparation); PROC (Process)
(**fusion** peptides, with **MHC class II** chimera with Ig Fc fragment; prepn. and T-cell cytolytic activity of)
IT Autoimmune diseases
Graft vs. host reaction
(**fusion** proteins of **MHC class II** extracellular domains ahd Ig Fc.gamma.2a fragment and contg. peptide epitope relevant to)
IT Fc.gamma.RII receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(heterodimeric **fusion** proteins of **MHC class II** extracellular domains and Ig Fc.gamma.2a fragments and contg. peptide epitope bind to)
IT Immunotherapy
(of autoimmune disease or graft-vs.-host disease in relation to **fusion** proteins of **MHC class II** extracellular domains and Ig Fc.gamma.2a fragment and contg. disease-relevant peptide epitope)
IT HLA-DR antigen
HLA-DR2 antigen
HLA-DR4 antigen
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. and T-cell cytolytic activity of peptide **fusion** protein contg. **MHC class II** and Ig Fc.gamma.2a fragment in relation to)

L2 ANSWER 20 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:505628 CAPLUS
DOCUMENT NUMBER: 131:143514
TITLE: Interaction of MHC Class II proteins with members of the PCNA family of proteins
INVENTOR(S): Clayberger, Carol; Krensky, Alan M.
PATENT ASSIGNEE(S): Stanford University, USA
SOURCE: U.S., 10 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5935797	A	19990810	US 1997-829132	19970328
PRIORITY APPLN. INFO.:			US 1994-260548	19940616
			US 1996-741530	19961031

AB Present invention based on the identification of the mol. interaction that forms the basis of the immunosuppressive activity of peptides comprising residues 71-80 of an MHC Class II protein (Class II peptides). Specifically the present invention discloses that Class II peptides bind to members of the PCNA family of proteins. Based on this observation, present invention provides methods for identifying agents that can be used to modulate immune system activity.
REFERENCE COUNT: 20
REFERENCE(S): (1) Anon; WO 94/04171 1994 CAPLUS
(2) Anon; WO 94/20127 1994 CAPLUS
(3) Anon; WO 96/35715 1996 CAPLUS
(4) Chicz, R; Immunol Today 1994, V15, P155 CAPLUS
(5) Chicz, R; International Immunol 1994, V6, P1639 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT **Fusion** proteins (**chimeric** proteins)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interaction of **MHC Class II** proteins with members of the PCNA family of proteins for identification of immunosuppressive agent)

L2 ANSWER 21 OF 83 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999342066 MEDLINE
DOCUMENT NUMBER: 99342066 PubMed ID: 10411923
TITLE: Induction of hyporesponsiveness to intact foreign protein via retroviral-mediated gene expression: the IgG scaffold is important for induction and maintenance of immune hyporesponsiveness.
AUTHOR: Kang Y; Melo M; Deng E; Tisch R; El-Amine M; Scott D W
CORPORATE SOURCE: Department of Immunology, Holland Laboratory of the American Red Cross, Rockville, MD 20855, USA.
CONTRACT NUMBER: AI26961 (NIAID)
AI35622 (NIAID)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Jul 20) 96 (15) 8609-14.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990823
AB IgG molecules can be highly tolerogenic carriers for associated antigens. Previously, we reported that recipients of bone marrow or lipopolysaccharide-stimulated B-cell blasts, both of which were retrovirally gene-transferred with an immunodominant peptide in-frame with the variable region of a murine IgG heavy chain, were rendered profoundly unresponsive to that epitope. To further investigate whether tolerance to larger molecules can be achieved via this approach and whether the IgG scaffold is important for induction and maintenance of immunological tolerance, we engineered two retroviral constructs encoding the cI lambda repressor (MBAE-1-102 and MBAE-1-102-IgG) for gene transfer. Our results show that recipients of bone marrow or peripheral B cells, transduced with

the MBAE-1-102-IgG recombinant, are hyporesponsive to p1-102. In addition, the self-IgG scaffold enhanced the induction and maintenance of such an immune hyporesponsiveness. Thus, our studies demonstrate that in vivo-expressed IgG heavy chain **fusion** protein can be processed and presented on the appropriate **MHC class II**, resulting in hyporesponsiveness to that antigen and offering an additional therapeutic approach to autoimmune diseases.

AB . . . enhanced the induction and maintenance of such an immune hyporesponsiveness. Thus, our studies demonstrate that in vivo-expressed IgG heavy chain **fusion** protein can be processed and presented on the appropriate **MHC class II**, resulting in hyporesponsiveness to that antigen and offering an additional therapeutic approach to autoimmune diseases.

L2 ANSWER 22 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:82337 CAPLUS
DOCUMENT NUMBER: 132:206247
TITLE: Identification of heterologous translocation partner genes fused to the BCL6 gene in diffuse large B-cell lymphomas: 5'-RACE and LA-PCR analyses of biopsy samples
AUTHOR(S): Yoshida, Shoko; Kaneita, Yoshitaka; Aoki, Yutaka; Seto, Masao; Mori, Shigeo; Moriyama, Masatsugu
CORPORATE SOURCE: Department of Pathology, Institute of Medical Science, The University of Tokyo, Tokyo, Japan
SOURCE: Oncogene (1999), 18(56), 7994-7999
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To elucidate the mol. mechanism(s) for BCL6 translocation, the authors identified translocational partner genes by subjecting clin. biopsy samples from patients with non-Hodgkin's lymphoma to 5'-rapid amplification of cDNA ends (5'-RACE). Sequence anal. of the 5'-RACE product revealed that the BCL6 gene was fused to the J segment of the Ig heavy chain (IgH) gene in about half of the cases, but in the other half, it was fused to heterologous partners, including the MHC class II transactivator (CIITA), pim-1, eukaryotic initiation factor 4AII (eif4AII), transferrin receptor (TFRR) and ikaros genes. Since analyses using genomic long and accurate (LA)-PCR revealed that the breakpoints in the partner gene were confined to the first intron or the second exon in all cases, the promoter and the first exon of the BCL6 gene were replaced by the promoter and the first or both the first and second exon of the partner gene. The breakpoint flanking sequences had no recombination signal sequences (RSSs) or chi sequences and were homologous with the switch region only when the BCL6 gene was fused to the IgH gene, suggesting that BCL6 translocation cannot be explained solely by mistakes of V(D)J, or chi-mediated or class-switch recombination, but rather another mechanism may also be required to explain the mol. mechanism for the promiscuous BCL6 translocation.

REFERENCE COUNT: 33
REFERENCE(S): (1) Akasaka, T; Cancer Res 1997, V57, P7 CAPLUS
(2) Baron, B; Proc Natl Acad Sci USA 1993, V90, P5262 CAPLUS
(3) Bastard, C; Blood 1994, V83, P2423 CAPLUS
(5) Chen, W; Blood 1998, V91, P603 CAPLUS
(6) Cleary, M; Proc Natl Acad Sci USA 1985, V82, P7439 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Transcription factors
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(CIITA (**MHC class II** transactivator), **fusion** protein; heterologous translocation partner genes fused to BCL6 gene in diffuse large B-cell lymphomas in humans)

L2 ANSWER 23 OF 83 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1999282935 MEDLINE
DOCUMENT NUMBER: 99282935 PubMed ID: 10352267
TITLE: Ig alpha and Ig beta are required for efficient trafficking to late endosomes and to enhance antigen presentation.
AUTHOR: Siemasko K; Eisfelder B J; Stebbins C; Kabak S; Sant A J; Song W; Clark M R
CORPORATE SOURCE: Section of Rheumatology, Department of Medicine, Committee on Immunology, University of Chicago, IL 60637, USA.
CONTRACT NUMBER: 5T32HL0738117 (NHLBI)
GM52736 (NIGMS)
GM56187 (NIGMS)
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Jun 1) 162 (11) 6518-25.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 20000303
Entered Medline: 19990616

AB The B cell Ag receptor (BCR) is a multimeric complex, containing Ig alpha and Ig beta, capable of internalizing and delivering specific Ags to specialized late endosomes, where they are processed into peptides for loading onto MHC class II molecules. By this mechanism, the presentation of receptor-selected epitopes to T cells is enhanced by several orders of magnitude. Previously, it has been reported that, under some circumstances, either Ig alpha or Ig beta can facilitate the presentation of Ags. However, we now demonstrate that if these Ags are at low concentrations and temporally restricted, both Ig alpha and Ig beta are required. When compared with the BCR, chimeric complexes containing either chain alone were internalized but failed to access the **MHC class II**-enriched compartment (MIIC) or induce the aggregation and **fusion** of its constituent vesicles. Furthermore, Ig alpha/Ig beta complexes in which the immunoreceptor tyrosine-based activation motif tyrosines of Ig alpha were mutated were also incapable of accessing the MIIC or of facilitating the presentation of Ag. These data indicate that both Ig alpha and Ig beta contribute signaling, and possibly other functions, to the BCR that are necessary and sufficient to reconstitute the trafficking and Ag-processing enhancing capacities of the intact receptor complex.

AB . . . are required. When compared with the BCR, chimeric complexes containing either chain alone were internalized but failed to access the **MHC class II**-enriched compartment (MIIC) or induce the aggregation and **fusion** of its constituent vesicles.

Furthermore, Ig alpha/Ig beta complexes i[illegible]ich the immunoreceptor tyrosine-based activation motif tyrosines of Ig alpha. . .

L2 ANSWER 24 OF 83 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1999384071 MEDLINE
DOCUMENT NUMBER: 99384071 PubMed ID: 10452991
TITLE: Polarized transport of MHC class II molecules in Madin-Darby canine kidney cells is directed by a leucine-based signal in the cytoplasmic tail of the beta-chain.
AUTHOR: Simonsen A; Pedersen K W; Nordeng T W; von der Lippe A; Stang E; Long E O; Bakke O
CORPORATE SOURCE: Department of Biology, University of Oslo, Norway.
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Sep 1) 163 (5) 2540-8. Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990925
Last Updated on STN: 19990925
Entered Medline: 19990914

AB MHC class II molecules are found on the basolateral plasma membrane domain of polarized epithelial cells, where they can present Ag to intraepithelial lymphocytes in the vascular space. We have analyzed the sorting information required for efficient intracellular localization and polarized distribution of MHC class II molecules in stably transfected Madin-Darby canine kidney cells. These cells were able to present influenza virus particles to HLA-DR1-restricted T cell clones. Wild-type MHC class II molecules were located on the basolateral plasma membrane domain, in basolateral early endosomes, and in late multivesicular endosomes, the latter also containing the **MHC class** II-associated invariant chain and an HLA-DM **fusion** protein. A phenylalanine-leucine residue within the cytoplasmic tail of the beta-chain was required for basolateral distribution, efficient internalization, and localization of the MHC class II molecules to basolateral early endosomes. However, distribution to apically located, late multivesicular endosomes did not depend on signals in the class II cytoplasmic tails as both wild-type class II molecules and mutant molecules lacking the phenylalanine-leucine motif were found in these compartments. Our results demonstrate that sorting information in the tails of class II dimers is an absolute requirement for their basolateral surface distribution and intracellular localization.

AB . . . on the basolateral plasma membrane domain, in basolateral early endosomes, and in late multivesicular endosomes, the latter also containing the **MHC class II**-associated invariant chain and an HLA-DM **fusion** protein. A phenylalanine-leucine residue within the cytoplasmic tail of the beta-chain was required for basolateral distribution, efficient internalization, and localization. . .

L2 ANSWER 25 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:726049 CAPLUS
DOCUMENT NUMBER: 132:34439
TITLE: C-terminal extension of the MHC class II-associated invariant chain by an antigenic sequence triggers activation of naive T cells
AUTHOR(S): Sponaas, A. M.; Carstens, C.; Koch, N.
CORPORATE SOURCE: Division of Immunobiology, University of Bonn, Bonn, D-53117, Germany
SOURCE: Gene Ther. (1999), 6(11), 1826-1834
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In vitro and in vivo activation of T cells was investigated with invariant chain-antigen fusion protein. The CD4 T cell epitope amino acid 52-61 of hen egg lysozyme (HEL) was attached to the C-terminal end of invariant chain (Ii). Expression of this recombinant Ii HEL directs the T cell epitope to the class II processing pathway. Class II mols. of transfected antigen presenting cells (APC) are charged with this HEL epitope. The endogenously provided epitope competes with processing and presentation of exogenously added antigen. APC expressing recombinant Ii HEL stimulate a maximal IL-2 response of HEL-specific T hybridoma cells. Non-professional APC expressing recombinant Ii HEL and H2-Ak are also able to activate naive T cells from 3A9 TCR transgenic mice, a result not achieved with peptide pulsed APC. To elicit an in vivo immune response dendritic cells (DC) were transfected with rIi HEL cDNA: following immunization of CBA mice with transfected DC, a primary T cell response against the HEL epitope was induced. Thus the procedure described here could be used to introduce antigens into the class II processing pathway and to elicit T cell activation both in vitro and in vivo.

REFERENCE COUNT: 52
REFERENCE(S): (1) Akbari, O; J Exp Med 1999, V189, P169 CAPLUS
(2) Allen, P; J Immunol 1985, V135, P368 CAPLUS
(3) Avva, R; Immunity 1994, V1, P763 CAPLUS
(4) Bakke, O; Cell 1990, V63, P707 CAPLUS
(5) Banchereau, J; Nature 1998, V392, P245 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Histocompatibility antigens
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(I-Ak; invariant chain-antigenic peptide **fusion** constructs trigger activation of naive T-cells via **MHC class II** pathway)
IT Antigen-presenting cell
Dendritic cell
(**MHC class II** pathway-mediated processing and presentation of invariant chain-antigenic peptide **fusion** constructs by)
IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(fusion peptides, with invariant chain; invariant chain-antigenic peptide **fusion** constructs trigger activation of naive T-cells via **MHC class II** pathway)
IT Invariant chain (class II antigen)
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(fusion products, with antigenic peptides; invariant chain-antigenic peptide **fusion** constructs trigger activation of naive T-cells via **MHC class II** pathway)
IT Fusion proteins (chimeric proteins)

RL: BAC (Biological activity or ef [illegible]ept adverse); BIOL (Biological study)
(invariant chain-antigenic peptide **fusion** constructs trigger activation of naive T-cells via **MHC class** II pathway)
IT Antigen presentation
Antigen processing
(of invariant chain-antigenic peptide **fusion** constructs via **MHC class II** pathway)

L2 ANSWER 26 OF 83 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1999328195 MEDLINE
DOCUMENT NUMBER: 99328195 PubMed ID: 10401768
TITLE: Anti-major histocompatibility complex class II treatment prevents graft rejection in the hamster-to-rat cardiac xenograft.
COMMENT: Comment in: Transplantation. 1999 Jun 27;67(12):1515-6
AUTHOR: Saxton N E; Hallaway R V; Ladyman H M; Janczynski B T; Nesbitt A M; Zinkewich-Peotti K; Smith R; Foulkes R
CORPORATE SOURCE: Celltech Therapeutics Ltd., Slough, Berks, UK.
SOURCE: TRANSPLANTATION, (1999 Jun 27) 67 (12) 1599-606.
Journal code: WEJ; 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990730
Last Updated on STN: 19990730
Entered Medline: 19990720

AB BACKGROUND: Several groups have achieved graft acceptance in the concordant hamster to rat model by using a combination of anti-proliferative drugs and conventional immunosuppressive therapy. However, such aggressive treatment often leads to the recipient dying with a functional xenograft, as a result of opportunistic infections. This study aimed to investigate the effects of a short course of therapy with an anti-**MHC class II** monoclonal antibody treatment (**chimeric** OX6 [cOX6]) in combination with cyclosporin A (CyA) in a concordant hamster-to-rat xenograft model. METHODS: Rats receiving hamster cardiac xenografts were given CyA or cOX6 alone or in combination and were monitored daily to assess the effect of treatment on graft survival. Additional studies monitored the effect of treatment on the production of cytolytic anti-hamster antibodies by the recipient and the deposition of immunoglobulin (Ig)M and complement factors within the xenograft. RESULTS: Treatment with CyA only had no effect on graft survival, whereas treatment with cOX6 increased graft survival time by 2 days. The median graft survival time for cOX6+CyA was 76 days. cOX6 treatment of rats having undergone transplants inhibited the rise in cytotoxic anti-hamster antibodies in peripheral blood until day 5, whereas combination therapy completely inhibited anti-hamster antibody formation. Fluorescence-activated cell sorter analysis showed treatment with cOX6 significantly reduced circulating B cell numbers until day 5. Anti-MHC class II treatment also markedly reduced the deposition of both IgM and C3. Anti-MHC class II treatment with CyA gives long term survival in concordant xenografts without severe side effects. CONCLUSIONS: The mechanism of action of this combination is complex and could be caused by an initial inhibition of B cell function by the anti-MHC class II treatment and the subsequent inhibition of T cell dependent pathways by CyA.
AB . . . a result of opportunistic infections. This study aimed to investigate the effects of a short course of therapy with an anti-**MHC class II** monoclonal antibody treatment (**chimeric** OX6 [cOX6]) in combination with cyclosporin A (CyA) in a concordant hamster-to-rat xenograft model. METHODS: Rats receiving hamster cardiac xenografts. . .

L2 ANSWER 27 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:477237 CAPLUS
DOCUMENT NUMBER: 131:270809
TITLE: Anti-major histocompatibility complex class II treatment prevents graft rejection in the hamster-to-rat cardiac xenograft
AUTHOR(S): Saxton, Nina E.; Hallaway, Rhona V.; Ladyman, Heather M.; Janczynski, Barbara T.; Nesbitt, Andrew M.; Zinkewich-Peotti, Karen; Smith, Richard; Foulkes, Roland
CORPORATE SOURCE: Celltech Therapeutics Ltd, Berks, SL1 4EN, UK
SOURCE: Transplantation (1999), 67(12), 1598-1606
CODEN: TRPLAU; ISSN: 0041-1337
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several groups have achieved graft acceptance in the concordant hamster to rat model by using a combination of anti-proliferative drugs and conventional immunosuppressive therapy. However, such aggressive treatment often leads to the recipient dying with a functional xenograft, as a result of opportunistic infections. This study aimed to investigate the effects of a short course of therapy with an anti-**MHC class II** monoclonal antibody treatment (**chimeric** OX6 [cOX6]) in combination with cyclosporin A (CyA) in a concordant hamster-to-rat xenograft model. Rats receiving hamster cardiac xenografts were given CyA or cOX6 alone or in combination and were monitored daily to assess the effect of treatment on graft survival. Addnl. studies monitored the effect of treatment on the prodn. of cytolytic antihamster antibodies by the recipient and the deposition of IgM and complement factors within the xenograft. Treatment with CyA only had no effect on graft survival, whereas treatment with cOX6 increased graft survival time by 2 days. The median graft survival time for cOX6+CyA was 76 days. The cOX6 treatment of rats having undergone transplants inhibited the rise in cytotoxic anti-hamster antibodies in peripheral blood until day 5, whereas combination therapy completely inhibited anti-hamster antibody formation. Fluorescence-activated cell sorter anal. showed treatment with cOX6 significantly reduced circulating B cell nos. until day 5. Anti-MHC class II treatment also markedly reduced the deposition of both IgM and C3. Anti-MHC class II treatment with CyA gives long term survival in concordant xenografts without severe side effects. The mechanism of action of this combination is complex and could be caused by an initial inhibition of B cell function by the anti-MHC class II treatment and the subsequent inhibition of T cell dependent pathways by CyA.
REFERENCE COUNT: 24
REFERENCE(S): (1) Andre, P; J Exp Med 1994, V179, P763 CAPLUS
(2) Bonagura, V; Cell Immunol 1985, V96, P442 CAPLUS
(5) Forsgren, S; Scand J Immunol 1987, V25(3), P225

CAPLUS
(6) Fukumoto, T; Eur J Immunol 1982, V12, P237 CAPLUS
(14) Priestley, C; Transplantation 1992, V53(5), P1024
CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Several groups have achieved graft acceptance in the concordant hamster to rat model by using a combination of anti-proliferative drugs and conventional immunosuppressive therapy. However, such aggressive treatment often leads to the recipient dying with a functional xenograft, as a result of opportunistic infections. This study aimed to investigate the effects of a short course of therapy with an anti-**MHC class II** monoclonal antibody treatment (**chimeric** OX6 [cOX6]) in combination with cyclosporin A (CyA) in a concordant hamster-to-rat xenograft model. Rats receiving hamster cardiac xenografts were given CyA or cOX6 alone or in combination and were monitored daily to assess the effect of treatment on graft survival. Addnl. studies monitored the effect of treatment on the prodn. of cytolytic antihamster antibodies by the recipient and the deposition of IgM and complement factors within the xenograft. Treatment with CyA only had no effect on graft survival, whereas treatment with cOX6 increased graft survival time by 2 days. The median graft survival time for cOX6+CyA was 76 days. The cOX6 treatment of rats having undergone transplants inhibited the rise in cytotoxic anti-hamster antibodies in peripheral blood until day 5, whereas combination therapy completely inhibited anti-hamster antibody formation. Fluorescence-activated cell sorter anal. showed treatment with cOX6 significantly reduced circulating B cell nos. until day 5. Anti-MHC class II treatment also markedly reduced the deposition of both IgM and C3. Anti-MHC class II treatment with CyA gives long term survival in concordant xenografts without severe side effects. The mechanism of action of this combination is complex and could be caused by an initial inhibition of B cell function by the anti-MHC class II treatment and the subsequent inhibition of T cell dependent pathways by CyA.

L2 ANSWER 28 OF 83 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1999167366 MEDLINE
DOCUMENT NUMBER: 99167366 PubMed ID: 10066451
TITLE: SEA-scFv as a bifunctional antibody: construction of a bacterial expression system and its functional analysis.
COMMENT: Erratum in: Biochem Biophys Res Commun 1999 May 27;259(1):230
AUTHOR: Sakurai N; Kudo T; Suzuki M; Tsumoto K; Takemura S; Kodama H; Ebara S; Teramae A; Katayose Y; Shinoda M; Kurokawa T; Hinoda Y; Imai K; Matsuno S; Kumagai I
CORPORATE SOURCE: Tohoku University School of Medicine, Tohoku University, Sendai, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1999 Mar 5) 256 (1) 223-30.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 20000303
Entered Medline: 19990413

AB A SEA-antibody single chain Fv (SEA-scFv) fusion protein was produced by bacterial expression system in this study. SEA-scFv has both staphylococcal enterotoxin A (SEA) effects and antibody activity directed at the epithelial mucin core protein MUC1, a cancer associated antigen. It was expressed mostly in the cytoplasm as an insoluble form. The gene product was solubilized by guanidine hydrochloride, refolded by conventional dilution method, and purified using metal-chelating chromatography. The resulting SEA-scFv **fusion** protein preparation was found to react with MUC1 and **MHC class** II antigens and had the ability to enhance cytotoxicity of lymphokine activated killer cells with a T cell phenotype against a human bile duct carcinoma cell line, TFK-1, expressing MUC1. This genetically engineered SEA-scFv fusion protein promises to be an important reagent for cancer immunotherapy.
Copyright 1999 Academic Press.

AB . . . gene product was solubilized by guanidine hydrochloride, refolded by conventional dilution method, and purified using metal-chelating chromatography. The resulting SEA-scFv **fusion** protein preparation was found to react with MUC1 and **MHC class** II antigens and had the ability to enhance cytotoxicity of lymphokine activated killer cells with a T cell phenotype against a. . .

L2 ANSWER 29 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:191154 CAPLUS
DOCUMENT NUMBER: 131:57491
TITLE: Soluble, high-affinity dimers of T-cell receptors and class II major histocompatibility complexes: Biochemical probes for analysis and modulation of immune responses
AUTHOR(S): Lebowitz, Michael S.; O'Herrin, Sean M.; Hamad, Abdel-Rahim A.; Fahmy, Tarek; Marguet, Didier; Barnes, Nicholas C.; Pardoll, Drew; Bieler, Joan G.; Schneck, Jonathan P.
CORPORATE SOURCE: Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
SOURCE: Cell. Immunol. (1999), 192(2), 175-184
CODEN: CLIMB8; ISSN: 0008-8749
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB T cell receptors (TCR) and major histocompatibility complex (MHC) mols. are integral membrane proteins that have central roles in cell-mediated immune recognition. Therefore, sol. analogs of these mols. would be useful for analyzing and possibly modulating antigen-specific immune responses. However, due to the intrinsic low-affinity and inherent soly. problems, it has been difficult to produce sol. high-affinity analogs of TCR and class II MHC mols. This report describes a general approach which solves this intrinsic low-affinity by constructing sol. divalent analogs using IgG as a mol. scaffold. The divalent nature of the complexes increases the avidity of the chimeric mols. for cognate ligands. The generality of this approach was studied by making sol. divalent analogs of two different classes of proteins, a TCR (2C TCR2Ig) and a class II MHC (MCCI-Ek2Ig) mol. Direct flow cytometry assays demonstrate that the divalent 2C TCR2Ig chimera retained the specificity of the native 2C TCR, while displaying increased avidity for cognate peptide/MHC ligands, resulting in a high-affinity probe capable of detecting interactions that heretofore have only been detected using surface plasmon resonance.

TCR2IgG was also used in immunofluorescence studies to show ER localization of intracellular peptide-MHC complexes after peptide feeding. MCCI-Ek2Ig chimeras were able to both stain and activate an MCC-specific T cell hybridoma. Construction and expression of these two diverse heterodimers demonstrate the generality of this approach. Furthermore, the increased avidity of these sol. divalent proteins makes these chimeric mols. potentially useful in clin. settings for probing and modulating in vivo cellular responses. (c) 1999 Academic Press.

REFERENCE COUNT: 42
REFERENCE(S):
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(2) Altman, J; Proc Natl Acad Sci USA 1993, V90, P10330 CAPLUS
(3) Altman, J; Science 1996, V274, P94 CAPLUS
(5) Arimilli, S; J Biol Chem 1995, V270, P971 CAPLUS
(6) Brodnicki, T; Mol Immunol 1996, V33, P253 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ST TCR receptor Ig fusion protein; **MHC class II** Ig **fusion** protein

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(Gl, **fusion** products, with TCR receptors or **MHC class II**; prepn. and biol. activity of sol. high-affinity dimers of T-cell receptors and class II MHC)

L2 ANSWER 30 OF 83 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1999157965 MEDLINE
DOCUMENT NUMBER: 99157965 PubMed ID: 10050678
TITLE: Cellular distribution of a mixed **MHC class II** heterodimer between DRalpha and a **chimeric** DObeta chain.
AUTHOR: Samaan A; Thibodeau J; Mahana W; Castellino F; Cazenave P A; Kindt T J
CORPORATE SOURCE: Laboratory of Immunogenetics, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD 20852, USA.
SOURCE: INTERNATIONAL IMMUNOLOGY, (1999 Jan) 11 (1) 99-111.
Journal code: AY5; 8916182. ISSN: 0953-8178.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990511

AB Human MHC class II antigens include HLA-DR, -DQ, and -DP molecules that present antigens to CD4+ T cells, as well as the non-classical molecules HLA-DM and -DO. HLA-DM promotes peptide binding to class II molecules in endocytic compartments and HLA-DO, which is physically associated with HLA-DM in B lymphocytes, regulates HLA-DM function. Antibodies specific for the DObeta chain were obtained by immunization of mice with a heterodimer consisting of a chimeric DObeta chain (DR/DObeta), containing 18 N-terminal residues of DRbeta, paired with the DRalpha chain and isolated from transfected murine fibroblasts. The specificity of this serum for the DObeta chain and the lysosomal expression of the HLA-DO protein was confirmed using mutant human B cell lines lacking DR or DO molecules. The lysosomal localization of HLA-DO in human B cells contrasts with the cell surface expression of the mixed pair in transfected murine fibroblasts and raises questions concerning the role of the putative targeting motifs in HLA-DO. Transfection of the chimeric DR/DObeta chain along with DRalpha into human epithelial HeLa cells resulted in high levels of expression of the mixed isotypic pair at the surface of transfectants as well as in lysosomes. The same pattern was observed in HeLa cells transfected with the DObeta chimera and a DRa chain lacking the cytoplasmic tail. Taken together, these results suggest that functional sorting motifs exist in the DObeta chain but that the tight compartmentalization of HLA-DO observed inside B lymphocytes is controlled by the HLA-DOalpha chain and HLA-DM.

TI Cellular distribution of a mixed **MHC class II** heterodimer between DRalpha and a **chimeric** DObeta chain.

L2 ANSWER 31 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:126278 CAPLUS
DOCUMENT NUMBER: 128:191578
TITLE: Soluble monovalent and multivalent **MHC class II fusion** proteins, and uses therefor
INVENTOR(S): Wucherpfennig, Kai W.; Strominger, Jack L.
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA; Wucherpfennig, Kai W.; Strominger, Jack L.
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9806749	A2	19980219	WO 1997-US14503	19970815
W: AU, CA, JP, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9740723	A1	19980306	AU 1997-40723	19970815
AU 730457	B2	20010308		
EP 935607	A2	19990818	EP 1997-938386	19970815
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000516470	T2	20001212	JP 1998-510100	19970815
PRIORITY APPLN. INFO.:			US 1996-24077 P	19960816
			WO 1997-US14503 W	19970815

AB The present invention is directed to the design, prodn., and use of recombinant fusion proteins derived, in part, from the proteins of the human Major Histocompatibility Complex. The MHC II fusion proteins are useful for treating autoimmune diseases, e.g. multiple sclerosis or rheumatoid arthritis. The MHC class II includes HLA-DR1, HLA-DR2, HLA-DR4, HLA-DQ1, HLA-DQ2, and HLA-DQ8 .alpha. chain or .beta. chain. Thus, DRA*0101 extracellular region-Fos leucine zipper domain and DRB1*1501 extracellular region-Jun leucine zipper domain fusion proteins, HLA-DR2 heterodimers (both DR.alpha. and DR.beta.), DR2-IgG fusion protein, and DR2-IgM fusion protein were prepd. The prepd. DR2-Ig. fusion proteins were used for selective depletion of T cells, or were complexed to toxins for inducing apoptosis of selective T cells.

TI Soluble monovalent and multivalent [redacted] class
II **fusion** proteins, and uses therefor
ST **MHC class II** Ig **fusion** protein
IT Flow cytometry
(FACS (fluorescence-activated cell sorting); sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT HLA-DQ antigen
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HLA-DQ1 antigen, **fusion** proteins; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT HLA-DQ antigen
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HLA-DQ2 antigen, **fusion** proteins; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT HLA-DQ antigen
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HLA-DQ8 antigen, **fusion** proteins; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Genes (animal)
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HLA-DQA1, **fusion** proteins; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Genes (animal)
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HLA-DQB1, **fusion** proteins; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Genes (animal)
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HLA-DRA, **fusion** proteins; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Genes (animal)
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HLA-DRB, **fusion** proteins; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT **Fusion** proteins (**chimeric** proteins)
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(MHC II; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Apoptosis
(T cell; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Immunity
(adoptive; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugate; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Immunoglobulin heavy chains
Immunoglobulin light chains
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(const. region **fusion** proteins; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT T cell (lymphocyte)
(depletion; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Class II MHC antigens
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**fusion** protein; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT HLA-DR1 antigen
HLA-DR2 antigen
HLA-DR4 antigen
IgA
IgD
IgE
IgG
IgG2a
IgM
c-fos gene (animal)
c-jun gene (animal)
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**fusion** proteins; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Skin diseases
(pemphigus vulgaris; sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Autoimmune diseases
Leucine zipper
Multiple sclerosis
Rheumatoid arthritis
Systemic lupus erythematosus
(sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT Immunoglobulin **fusion** products
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(sol. monovalent and multivalent **MHC class II fusion** proteins for treating autoimmune diseases)
IT TCR (T cell receptors)

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(sol. monovalent and multivalent MHC class II fusion proteins for treating autoimmune diseases)

IT Myelin basic protein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sol. monovalent and multivalent MHC class II fusion proteins for treating autoimmune diseases)

IT 203592-10-3 203592-12-5
RL: PRP (Properties)
(amino acid sequence; sol. monovalent and multivalent MHC class II fusion proteins for treating autoimmune diseases)

IT 203592-09-0 203592-11-4 203592-13-6 203592-14-7
RL: PRP (Properties)
(nucleotide sequence; sol. monovalent and multivalent MHC class II fusion proteins for treating autoimmune diseases)

L2 ANSWER 32 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:734956 CAPLUS
DOCUMENT NUMBER: 129:314972
TITLE: Enhancing the binding affinity of peptides for MHC class II molecules.
INVENTOR(S): Nag, Bishwajit
PATENT ASSIGNEE(S): Anergen Inc., USA
SOURCE: U.S., 24 pp. Cont.-in-part of U.S. Ser. No. 227,372.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5824315	A	19981020	US 1996-640344	19960430
US 5763585	A	19980609	US 1994-227372	19940414
US 6090587	A	20000718	US 1995-470535	19950606
EP 973547	A1	20000126	EP 1997-919885	19970318

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.:
US 1993-143575 B2 19931025
US 1994-227372 A2 19940414
US 1994-329010 A2 19941025
US 1993-136216 B2 19931013
US 1996-640344 A 19960430
WO 1997-US4360 W 19970318

AB This invention provides methods of improving the binding affinity of a peptide epitope for MHC class II mols. by attaching to the N-terminus of the peptide epitope a hydrophobic amino acid or a peptide contg. a hydrophobic amino acid. In one example, a peptide fragment of myelin basic protein, modified with an N-terminal tyrosine, exhibits enhanced binding to HLA-DR2. The invention also describes complexes between the modified antigenic peptides and MHC class II mols. (as single-chain constructs or fusion proteins) and their potential application in autoimmune disorders.

AB This invention provides methods of improving the binding affinity of a peptide epitope for MHC class II mols. by attaching to the N-terminus of the peptide epitope a hydrophobic amino acid or a peptide contg. a hydrophobic amino acid. In one example, a peptide fragment of myelin basic protein, modified with an N-terminal tyrosine, exhibits enhanced binding to HLA-DR2. The invention also describes complexes between the modified antigenic peptides and MHC class II mols. (as single-chain constructs or fusion proteins) and their potential application in autoimmune disorders.

IT Fusion proteins (chimeric proteins)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MHC class II with antigenic peptides; affinity of peptides for MHC class II mols. is enhanced by N-terminal modification with hydrophobic amino acids)

L2 ANSWER 33 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:180572 CAPLUS
DOCUMENT NUMBER: 128:242886
TITLE: Isolated Epstein-Barr virus BZLF2 proteins that bind MHC class II .beta. chain
INVENTOR(S): Alderson, Mark; Armitage, Richard J.; Cohen, Jeffrey I.; Comeau, Michael R.; Farrah, Theresa M.; Hutt-Fletcher, Lindsey M.; Spriggs, Melanie K.
PATENT ASSIGNEE(S): Immunex Corp., USA
SOURCE: U.S., 25 pp. Cont.-in-part of U.S. Ser. No. 235,397, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5726286	A	19980310	US 1995-430633	19950428
US 5925734	A	19990720	US 1997-936854	19970924

PRIORITY APPLN. INFO.:
US 1994-235397 19940428
US 1995-430633 19950428

AB Isolated viral proteins, and pharmaceutical compns. made therefrom, are disclosed which are capable of binding to a .beta. chain of a Class II Major Histocompatibility Complex antigen, thereby functioning to inhibit an antigen-specific response. The antigen-specific response-inhibiting viral protein and its fusion proteins are useful for preventing or treating autoimmune diseases, tissue or organ transplant rejection, and allergy or asthma. The viral proteins also have superantigen-like activity, and can be useful as superantigen and can be used for inhibition of EBV infection.

IT Fusion proteins (chimeric proteins)
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(isolated Epstein-Barr virus BZLF2 proteins that bind MHC class II .beta. chain)

L2 ANSWER 34 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:325081 CAPLUS
DOCUMENT NUMBER: 129:26773
TITLE: MHC class II-associated invariant chain peptide replacement by T cell epitopes. Engineered invariant

chain as a vehi directed and enhanced MHC class II antigen processing and presentation

AUTHOR(S): Malcherek, Georg; Wirblich, Christoph; Willcox, Nicholas; Rammensee, Hans-Georg; Trowsdale, John; Melms, Arthur

CORPORATE SOURCE: Department Neurology, Neuroimmunology Laboratory, University Tuebingen, Tuebingen, Germany

SOURCE: Eur. J. Immunol. (1998), 28(5), 1524-1533
CODEN: EJIMAF; ISSN: 0014-2980

PUBLISHER: Wiley-VCH Verlag GmbH

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Proteolysis of the invariant chain (Ii) leads to the generation of abundant MHC class II-assocd. invariant chain peptides (CLIP), which bind in the MHC class II binding groove via supermotifs in a manner similar to that of antigenic peptides. The authors have engineered an Ii vector with the capacity to express any antigenic peptide of interest instead of CLIP, for T cell stimulation. When peripheral blood mononuclear cells (PBMC) were pulsed with Ii hybrids encoding T cell epitopes of tetanus toxin or acetylcholine receptor, stimulation of T cells was dramatically enhanced compared to stimulation after priming with either the native or recombinant proteins. Site-specific insertion of antigenic sequences into the CLIP region promoted enhanced antigenicity of Ii hybrids which were shown to be processed intracellularly in a chloroquine-sensitive compartment. Naturally processed T helper epitopes were visualized directly on the surface of PBMC and identified as analogs of CLIP assocd. with MHC class II mols. This novel Ii vector provides a flexible and efficient system for the delivery of defined peptide epitopes to T cells which might be useful in the development of specific vaccines and in the study of intracellular processing.

IT **Fusion** proteins (**chimeric** proteins)
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(enhanced **MHC class II** antigen presentation using invariant chain engineered to express T-cell epitopes in CLIP peptides)

IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(**fusion** peptides, with invariant chain; enhanced **MHC class II** antigen presentation using invariant chain engineered to express T-cell epitopes in CLIP peptides)

IT Invariant chain (class II antigen)
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(**fusion** products, with antigenic peptides; enhanced **MHC class II** antigen presentation using invariant chain engineered to express T-cell epitopes in CLIP peptides)

L2 ANSWER 35 OF 83 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:417491 CAPLUS

DOCUMENT NUMBER: 129:160383

TITLE: Detection of antigen-specific T cells with multivalent soluble class II MHC covalent peptide complexes

AUTHOR(S): Crawford, Frances; Kozono, Haruo; White, Janice; Marrack, Philippa; Kappler, John

CORPORATE SOURCE: Division of Basic Immunology, National Jewish Medical and Research Center, Denver, CO, 80206, USA

SOURCE: Immunity (1998), 8(6), 675-682
CODEN: IUNIEH; ISSN: 1074-7613

PUBLISHER: Cell Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Multimeric sol. MHC class II mols. stably occupied with covalently attached peptides bind with appropriate specificity to T cell hybridomas and T cells from T cell receptor transgenic mice. There is a direct correlation between sol. T cell receptor affinity for monomeric MHC/peptide and level of binding of multimeric MHC/peptide to T cells. While binding of the multimeric MHC/peptide complex is proportional to T cell receptor affinity and expression level, there is little influence of T cell CD4.

IT Peptides, biological studies
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(**fusion** peptides, with **MHC class II** .beta. chain; detection of antigen-specific T cells with multivalent sol. class II MHC covalent peptide complexes)

L2 ANSWER 36 OF 83 MEDLINE DUPLICATE 13

ACCESSION NUMBER: 1998386416 MEDLINE

DOCUMENT NUMBER: 98386416 PubMed ID: 9719947

TITLE: Requirement of class II and membrane proximal region of mouse mammary tumor virus superantigen (Mtv SAG) in Mtv7 SAG presentation.

AUTHOR: Okamoto M; Kimura S; Katagiri M

CORPORATE SOURCE: Second Department of Pathology, Asahikawa Medical College, Japan.

SOURCE: HOKKAIDO IGAKU ZASSHI. HOKKAIDO JOURNAL OF MEDICAL SCIENCE, (1998 May) 73 (3) 205-14.
Journal code: GA9; 17410290R. ISSN: 0367-6102.

PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: Japanese

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199810

ENTRY DATE: Entered STN: 19981029
Last Updated on STN: 19981029
Entered Medline: 19981020

AB Although in some cases superantigens (SAGs) have been shown to bind directly to T cell receptor (TCR) in the absence of MHC molecules, the precise role of MHC class II in SAG presentation to T cells is not thoroughly understood. In particular, it is still not known whether MHC class II is a mere transporter of mouse mammary tumor virus (Mtv) SAG to the cell surface or an essential component complexed with SAGs for TCR triggering. In this study, we found that **MHC class II** negative B cell line transfected with CD72/Mtv7 sag **chimeric** gene could express the Mtv7 SAG on the cell surface. The murine B cell line M12.4.1 and its **MHC class II** negative mutant, M12C3 are transfected with CD72/Mtv7 sag **chimeric** gene. Although both transfectants expressed Mtv7 SAG on their cell surface, M12.4.1 but not M12C3 activated Mtv7 SAG responding T cell hybridomas. The results argue that the mere presence of Mtv7 SAG on the cell surface does not effectively transmit the signal to TCR. As MHC

class II-positive cells transfec[illegible]72/Mtv7 sag gene caused T cell activation, the cytoplasmic/trans[illegible]brane portion of Mtv7 SAG is not essential for T cell activation. In order to examine the importance of the membrane proximal region of Mtv7 SAG in T cell activation, we constructed chimeric genes between the encoding cytoplasmic/transmembrane portion of CD72 and N-truncated extracellular region of Mtv7 sag (CD72/ATG3, CD72/ATG5). Despite the expression of Mtv7 SAG on the cell surface, cells transfected with CD72/ATG3 or CD72/ATG5 genes were unable to stimulate Mtv7 SAG responding T cell hybridomas. The results indicate that 54 extracellular amino acids (the difference between CD72/Mtv 7 SAG and CD72/ATG3) located proximal to the membrane may be important for Mtv7 SAG function.

AB . . . to the cell surface or an essential component complexed with SAGs for TCR triggering. In this study, we found that **MHC class II** negative B cell line transfected with CD72/Mtv7 sag **chimeric** gene could express the Mtv7 SAG on the cell surface. The murine B cell line M12.4.1 and its **MHC class II** negative mutant, M12C3 are transfected with CD72/Mtv7 sag **chimeric** gene. Although both transfectants expressed Mtv7 SAG on their cell surface, M12.4.1 but not M12C3 activated Mtv7 SAG responding T. . .

L2 ANSWER 37 OF 83 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 1999074406 MEDLINE
DOCUMENT NUMBER: 99074406 PubMed ID: 9852214
TITLE: MHC class II-independent, Vbeta-specific activation of T cells by superantigen mutants fused to anti-tumor Fab fragments: implications for use in treatment of human colon carcinoma.
AUTHOR: Newton D W; Dohlsten M; Lando P A; Kalland T; Olsson C; Kotb M
CORPORATE SOURCE: Departments of Surgery, Microbiology and Immunology, University of Tennessee-Memphis, Memphis, TN 38163, USA.
CONTRACT NUMBER: AI-GM54892-06 (NIAID)
SOURCE: INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, (1998 Jan) 1 (1) 157-62.
Journal code: C8H; 9810955. ISSN: 1107-3756.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990326
Last Updated on STN: 19990326
Entered Medline: 19990316

AB Genetically engineered fusion proteins of the super-antigen staphylococcal enterotoxin A (SEA) and tumor-reactive monoclonal antibodies, C215Fab-SEA and C242Fab-SEA, have been generated and shown to be effective in mediating superantigen-antibody directed cellular cytotoxicity against human carcinoma cells expressing the CA215 or CA242 antigens in an MHC class II-independent manner. In an attempt to reduce the in vivo toxicity of superantigen administration, alanine substitution mutations in SEA at residues F47 and D227 that affect SEA binding to class II molecules have been created and genetically linked to C215Fab or C242Fab. The purpose of this study was to determine whether these Fab-SEA mutant **fusion** proteins, that have low **MHC class II** binding affinities, were still able to stimulate human T cells in a Vbeta-specific manner in the presence or absence of **MHC class II** molecules. The SEA wt- and SEA-D227A-based **fusion** proteins shared the ability to activate V beta5. 2-, Vbeta6-, Vbeta7-, Vbeta9- and Vbeta18-bearing T cells, whereas Fab-SEA-F47A protein activated only Vbeta6- and Vbeta7-bearing T cells. The fusion of Fab fragments onto SEA wt, SEA-F47A or SEA-D227A had no effect on the Vbeta specificity of these superantigens. Fab fusion proteins containing either SEA wt or SEA mutants were presented, in the absence of class II molecules, by CHO cells transfected with CA215 and CD80 and all induced the expansion of only Vbeta6-, Vbeta7- and Vbeta 18-bearing T cells. Fab-SEA mutant fusion proteins may provide attenuated therapeutic agents that, while still able to specifically target high affinity T cells for MHC class II-independent local tumor killing, will not induce excessive systemic toxicity.

AB . . . created and genetically linked to C215Fab or C242Fab. The purpose of this study was to determine whether these Fab-SEA mutant **fusion** proteins, that have low **MHC class II** binding affinities, were still able to stimulate human T cells in a Vbeta-specific manner in the presence or absence of **MHC class II** molecules. The SEA wt- and SEA-D227A-based **fusion** proteins shared the ability to activate V beta5. 2-, Vbeta6-, Vbeta7-, Vbeta9- and Vbeta18-bearing T cells, whereas Fab-SEA-F47A protein activated. . .

L2 ANSWER 38 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:114598 CAPLUS
DOCUMENT NUMBER: 128:191312
TITLE: Protein sorting within the MHC class II antigen-processing pathway
AUTHOR(S): Marks, Michael S.
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104-6082, USA
SOURCE: Immunol. Res. (1998), 17(1&2), 141-154
CODEN: IMRSEB; ISSN: 0257-277X
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 124 refs. Major histocompatibility complex (MHC) class II mols. are required for the presentation of antigenic peptides that are derived predominantly from internalized proteins. The assembly of MHC class II/peptide complexes occurs within endosomal compartments of antigen-presenting cells (APCs). Therefore, for assembly to occur, MHC class II mols., foreign proteins, and accessory mols. must be sorted to appropriate intracellular sites. The author's lab. is trying to understand how proteins are sorted to various antigen-processing compartments as well as to conventional endosomal organelles. Using chimeric marker proteins and a variety of biochem. and genetic approaches, the specificity of protein sorting and the mechanisms by which sorting signals are deciphered are being addressed. By using a similar chimeric protein approach to target endogenous proteins to distinct compartments, the authors hope to address the role of processing events in each compartment in the generation of MHC class II ligands.

IT **Fusion** proteins (**chimeric** proteins)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(protein sorting within MHC class II antigen processing pathway)

L2 ANSWER 39 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:533677 CAPLUS
DOCUMENT NUMBER: 127:204455
TITLE: Preparation and immunomodulatory activity of single-chain MHC mols.
INVENTOR(S): Rhode, Peter R.; Jiao, Jin-An; Burkhardt, Martin; Wong, Hing C.
PATENT ASSIGNEE(S): Dade International, Inc., USA; Rhode, Peter R.; Jiao, Jin-An; Burkhardt, Martin; Wong, Hing C.
SOURCE: PCT Int. Appl., 216 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9728191	A1	19970807	WO 1997-US1617	19970130
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5869270	A	19990209	US 1996-596387	19960131
CA 2244755	AA	19970807	CA 1997-2244755	19970130
AU 9722538	A1	19970822	AU 1997-22538	19970130
AU 729672	B2	20010208		
EP 877760	A1	19981118	EP 1997-905709	19970130
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000515363	T2	20001121	JP 1997-527863	19970130

PRIORITY APPLN. INFO.: US 1996-596387 A 19960131
WO 1997-US1617 W 19970130

AB The present invention relates to novel complexes of major histocompatibility complex (MHC) mols. and uses of such complexes. In one aspect, the invention relates to loaded MHC complexes that include at least one MHC mol. with a peptide-binding groove and a presenting peptide non-covalently linked to the MHC protein. In another aspect, the invention features single chain **MHC class II** peptide **fusion** complexes with a presenting peptide covalently linked to the peptide binding groove of the complex. MHC complexes are useful for a variety of applications including: (1) in vitro screens for identification and isolation of peptides that modulate activity of selected T cells, including peptides that are T cell receptor antagonists and partial agonists, and (2) methods for suppressing or inducing an immune response in a mammal.

AB The present invention relates to novel complexes of major histocompatibility complex (MHC) mols. and uses of such complexes. In one aspect, the invention relates to loaded MHC complexes that include at least one MHC mol. with a peptide-binding groove and a presenting peptide non-covalently linked to the MHC protein. In another aspect, the invention features single chain **MHC class II** peptide **fusion** complexes with a presenting peptide covalently linked to the peptide binding groove of the complex. MHC complexes are useful for a variety of applications including: (1) in vitro screens for identification and isolation of peptides that modulate activity of selected T cells, including peptides that are T cell receptor antagonists and partial agonists, and (2) methods for suppressing or inducing an immune response in a mammal.

IT IgG2b
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**fusion** products, with **MHC class II**; prepn. and immunomodulatory activity of single-chain MHC mols.)

IT 194549-26-3
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(as linker for single-chain **MHC class II** -peptide **fusion** mol.)

L2 ANSWER 40 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:532525 CAPLUS
DOCUMENT NUMBER: 127:118258
TITLE: Gene delivery vehicle targeting to cell using MHC or .beta.2-microglobulin fusion products with targeting ligands such as anti-transferrin mAB or EBV glycoprotein
INVENTOR(S): Chada, Sunil; Banks, Theresa; Moore, Margaret D.; Chang, Stephen M. W.
PATENT ASSIGNEE(S): Chiron Viagene, Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9724446	A2	19970710	WO 1996-US20295	19961220
WO 9724446	A3	19971023		
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 870040	A2	19981014	EP 1996-945228	19961220
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE, IE				
JP 2000503532	T2	20000328	JP 1997-524442	19961220

PRIORITY APPLN. INFO.: US 1995-580541 19951229
US 1995-9411 19951229
WO 1996-US20295 19961220

AB **Fusion** proteins composed of an MHC Class I, **MHC Class II**, or .beta.2 microglobulin, and a targeting ligand are disclosed. Also disclosed are nucleic acid mols. which encode such fusion proteins as well as suitable expression cassettes and host

cells. Also provided are methods for tar[redacted] gene delivery vehicle to a selected cell type utilizing gene delivery vehicles which contain on their surfaces one of the above-mentioned fusion proteins. One example included human HLA-A2 fusion product with the targeting ligand EBV GP350/220. The expression cassette pSC6/350-A2 was then used for insertion into 293E or 293 2-3 to make a packaging cell line. Another example used erythropoietin fused to B2M for cloning erythropoietin in Escherichia coli strain XA90.

AB **Fusion** proteins composed of an MHC Class I, MHC **Class II**, or .beta.2 microglobulin, and a targeting ligand are disclosed. Also disclosed are nucleic acid mols. which encode such fusion proteins as well as suitable expression cassettes and host cells. Also provided are methods for targeting a gene delivery vehicle to a selected cell type utilizing gene delivery vehicles which contain on their surfaces one of the above-mentioned fusion proteins. One example included human HLA-A2 fusion product with the targeting ligand EBV GP350/220. The expression cassette pSC6/350-A2 was then used for insertion into 293E or 293 2-3 to make a packaging cell line. Another example used erythropoietin fused to B2M for cloning erythropoietin in Escherichia coli strain XA90.

L2 ANSWER 41 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:773406 CAPLUS
DOCUMENT NUMBER: 128:60454
TITLE: Expression of the superantigen Mycoplasma arthritidis mitogen in Escherichia coli and characterization of the recombinant protein
AUTHOR(S): Knudtson, Kevin L.; Manohar, Muniraj; Joyner, David E.; Ahmed, Elsayed A.; Cole, Barry C.
CORPORATE SOURCE: Division of Rheumatology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, 84132, USA
SOURCE: Infect. Immun. (1997), 65(12), 4965-4971
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB M. arthritidis mitogen (MAM), is a sol. protein with classical superantigenic properties and is produced by an organism that causes an acute and chronic proliferative arthritis. Unfortunately, the process of obtaining purified MAM from M. arthritidis culture supernatants is extremely time-consuming and costly, and very little material is recovered. Thus, the authors' lab. has expressed MAM in E. coli by using a protein fusion expression system. The construction and expression of recombinant MAM (rMAM), as well as a comparison of the biol. properties of rMAM to those of native MAM, are discussed. Briefly, conversion of the 3 UGA codons to UGG codons was required to obtain full-length expression and mitogenic activity of rMAM. Antisera to native MAM recognized both rMAM and the fusion protein. The TCR receptor V.beta. and **MHC class II** receptor usages by rMAM and the **fusion** protein were identical to that of native MAM. In addn., the ability to induce suppression and form the superantigen bridge could also be demonstrated with rMAM. Importantly, dose-response expts. indicated that homogeneous native MAM and rMAM were of equal potency. Thus, MAM has been successfully expressed in E. coli, thereby creating a viable alternative to native MAM.

AB M. arthritidis mitogen (MAM), is a sol. protein with classical superantigenic properties and is produced by an organism that causes an acute and chronic proliferative arthritis. Unfortunately, the process of obtaining purified MAM from M. arthritidis culture supernatants is extremely time-consuming and costly, and very little material is recovered. Thus, the authors' lab. has expressed MAM in E. coli by using a protein fusion expression system. The construction and expression of recombinant MAM (rMAM), as well as a comparison of the biol. properties of rMAM to those of native MAM, are discussed. Briefly, conversion of the 3 UGA codons to UGG codons was required to obtain full-length expression and mitogenic activity of rMAM. Antisera to native MAM recognized both rMAM and the fusion protein. The TCR receptor V.beta. and **MHC class II** receptor usages by rMAM and the **fusion** protein were identical to that of native MAM. In addn., the ability to induce suppression and form the superantigen bridge could also be demonstrated with rMAM. Importantly, dose-response expts. indicated that homogeneous native MAM and rMAM were of equal potency. Thus, MAM has been successfully expressed in E. coli, thereby creating a viable alternative to native MAM.

L2 ANSWER 42 OF 83 MEDLINE
ACCESSION NUMBER: 97272141 MEDLINE
DOCUMENT NUMBER: 97272141 PubMed ID: 9126986
TITLE: Functional characterization of the interaction between the superantigen staphylococcal enterotoxin A and the TCR.
AUTHOR: Antonsson P; Wingren A G; Hansson J; Kalland T; Varga M; Dohlsten M
CORPORATE SOURCE: Pharmacia and Upjohn, Lund Research Center, Sweden.. per.antonsson@eu.pnu.com
SOURCE: JOURNAL OF IMMUNOLOGY, (1997 May 1) 158 (9) 4245-51.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970602
Last Updated on STN: 19970602
Entered Medline: 19970519

AB In this report, we show that despite an overall amino acid residue identity of more than 80% between the staphylococcal enterotoxins (SE) A and E, these proteins markedly differ in their absolute requirement for the MHC class II during T cell activation. The superantigens were produced as C215Fab-SE fusion proteins and analyzed for their ability to activate T cells in a MHC class II-independent manner, using C215 Ag expressing cell lines as pseudo super-APCs. C215Fab-SEA, but not C215Fab-SEE, induced T cell cytotoxicity and proliferation in these MHC class II-independent systems. Introduction of a region from SEA, comprising amino acids 20-27, to SEE transferred the ability to engage T cells in the absence of **MHC class II**. Analysis of the Vbeta specificity of the **chimeric** SEA/SEE molecules and a panel of SEA mutants demonstrated that the site for TCR interaction covers the edge surrounding the shallow cavity on top of the SEA molecule.

AB . . . region from SEA, comprising amino acids 20-27, to SEE transferred the ability to engage T cells in the absence of **MHC class II**. Analysis of the Vbeta specificity of the **chimeric** SEA/SEE molecules and a panel of SEA mutants demonstrated

that the site for TCR interaction covers t[redacted]e surrounding the. . .

L2 ANSWER 43 OF 83 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 97225980 MEDLINE
DOCUMENT NUMBER: 97225980 PubMed ID: 9122222
TITLE: Genetically engineered superantigens as tolerable antitumor agents.
AUTHOR: Hansson J; Ohlsson L; Persson R; Andersson G; Ilback N G; Litton M J; Kalland T; Dohlsten M
CORPORATE SOURCE: Lund Research Center, Pharmacia & Upjohn, Sweden.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Mar 18) 94 (6) 2489-94. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970506
Last Updated on STN: 19970506
Entered Medline: 19970424

AB Superantigens (SAg) are a family of bacterial and viral proteins with strong immunostimulatory properties. SAg bound to major histocompatibility complex (MHC) class II molecules activate a high frequency of T cells and represent the most potent known activators of T cells to date. To explore the use of SAg for T cell-based tumor therapy we have created a tumor-reactive SAg by engineering a fusion protein composed of a tumor-reactive mAb (C215Fab) and the bacterial SAg staphylococcal enterotoxin A (SEA). A point mutation D227A was introduced at the major MHC class II binding site in SEA to reduce systemic toxicity. Treatment of tumor bearing mice with the Fab-SEA D227A fusion protein resulted in profound antitumor effects with a markedly reduced toxicity as compared with the wild-type Fab-SEA fusion protein. The reduced toxicity was probably due to a weak distribution of the SEA D227A **fusion** protein in tissues with a high **MHC class II** expression and low systemic cytokine levels as exhibited in mice and rabbits. The data presented demonstrate the efficacy of immunoconjugates containing a mutated SAg in directing a T cell attack against tumor cells with minimal systemic immune activation.

AB . . . with the wild-type Fab-SEA fusion protein. The reduced toxicity was probably due to a weak distribution of the SEA D227A **fusion** protein in tissues with a high **MHC class II** expression and low systemic cytokine levels as exhibited in mice and rabbits. The data presented demonstrate the efficacy of immunoconjugates. . .

L2 ANSWER 44 OF 83 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 97211764 MEDLINE
DOCUMENT NUMBER: 97211764 PubMed ID: 9058731
TITLE: A superantigen-antibody fusion protein for T-cell immunotherapy of human B-lineage malignancies.
AUTHOR: Gidlof C; Dohlsten M; Lando P; Kalland T; Sundstrom C; Totterman T H
CORPORATE SOURCE: Department of Clinical Immunology, University Hospital, Uppsala, Sweden.
SOURCE: BLOOD, (1997 Mar 15) 89 (6) 2089-97. Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19980206
Entered Medline: 19970402

AB The bacterial superantigen staphylococcal enterotoxin A (SEA) is an efficient activator of cytotoxic T cells when presented on major histocompatibility complex (MHC) class II molecules of target cells. Our previous studies showed that such SEA-directed T cells efficiently lysed chronic B-lymphocytic leukemia (B-CLL) cells. Next, we made a mutated SEA-protein A (SEAm-PA) fusion protein with more than 1,000-fold reduced binding affinity for **MHC class II** compared with native SEA. The **fusion** protein was successfully used to direct T cells to B-CLL cells coated with different B lineage-directed monoclonal antibodies (MoAbs). In this communication, we constructed a recombinant anti-CD19-Fab-SEAm **fusion** protein. The **MHC class II** binding capacity of the SEA part was drastically reduced by a D227A point mutation, whereas the T-cell activation properties were retained. The Fab part of the fusion protein displayed a binding affinity for CD19+ cells in the nanomolar range. The anti-CD19-Fab-SEAm molecule mediated effective, specific, rapid, and perforin-like T-cell lysis of B-CLL cells at low effector to target cell ratios. Normal CD19+ B cells were sensitive to lysis, whereas CD34+ progenitor cells and monocytes/macrophages were resistant. A panel of CD19+ B-cell lines representing different B-cell developmental stages were efficiently lysed, and the sensitivity correlated with surface ICAM-1 expression. The anti-CD19-Fab-SEAm fusion protein mediated highly effective killing of tumor biopsy cells representing several types of B-cell non-Hodgkin's lymphoma (B-NHL). Humanized severe combined immune deficiency (SCID) mice carrying Daudi lymphoma cells were used as an in vivo therapy model for evaluation of the anti-CD19-Fab-SEAm fusion protein. Greater than 90% reduction in tumor weight was recorded in anti-CD19-Fab-SEAm-treated animals compared with control animals receiving an irrelevant Fab-SEAm fusion protein. The present results indicate that MoAb-targeted superantigens (SAgs) may represent a promising approach for T-cell-based therapy of CD19+ B-cell malignancies.

AB . . . (B-CLL) cells. Next, we made a mutated SEA-protein A (SEAm-PA) fusion protein with more than 1,000-fold reduced binding affinity for **MHC class II** compared with native SEA. The **fusion** protein was successfully used to direct T cells to B-CLL cells coated with different B lineage-directed monoclonal antibodies (MoAbs). In this communication, we constructed a recombinant anti-CD19-Fab-SEAm **fusion** protein. The **MHC class II** binding capacity of the SEA part was drastically reduced by a D227A point mutation, whereas the T-cell activation properties were. . .

L2 ANSWER 45 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:168597 CAPLUS
DOCUMENT NUMBER: 128:293720
TITLE: Engineering and characterization of a murine MHC class II-immunoglobulin chimera expressing an immunodominant CD4 T viral epitope

AUTHOR(S): Casares, Sofia; Bona, [redacted]tin A.; Brumeanu, Teodor D.
CORPORATE SOURCE: The Department of Microbiology, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Protein Eng. (1997), 10(11), 1295-1301
CODEN: PRENE9; ISSN: 0269-2139
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB T cells recognize peptides derived from the processing of proteins by antigen presenting cells (APCs) in assocn. with the major histocompatibility complex (MHC) mols. The authors have engineered a murine MHC class II antigen presenting mol. consisting of the extracellular domains of I-Ed.alpha. and I-Ed.beta. chains to which the CD4 T cell immunodominant epitope HA110-120 of the hemagglutinin (HA) of the A/PR/8/34 influenza virus was covalently linked at the N-terminus of the I-Ed.beta. chain. The HA110-120-I-Ed.alpha..beta. complex was dimerized by the Fc portion of an IgG2a linked at the C-terminus of the I-Ed.beta. chain. SF9 insect cells infected with baculovirus carrying both I-Ed.alpha. and HA110-120-I-Ed.beta.-Fc.gamma.2a genes, secreted a disulfide-stabilized dimer of the HA110-120-I-Ed.alpha..beta.-Fc.gamma.2a mol., designated as DEF. The chimeric mol. preserved the structural integrity of both MHC-peptide complex and Fc portion of IgG2a, and was able to: (i) bind specifically to the cognate T cell receptors (TCRs) and to the Ig Fc.gamma.RII receptor (FcR), (ii) induce complement-mediated cell cytotoxicity, and (iii) trigger early prodn. of IL-2 in cognate T cells. Chimeric antigen presenting mols. with these characteristics may represent a novel platform for the development of immunomodulatory agents of therapeutic use.

IT **Chimeric** genes.
Synthetic genes
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(animal; engineering and characterization of murine **MHC class II**-Ig chimera expressing immunodominant CD4 T viral epitope)

IT Genes (animal)
Hemagglutinins
I-Ek antigen
IgG2a
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**chimeric**; engineering and characterization of murine **MHC class II**-Ig chimera expressing immunodominant CD4 T viral epitope)

IT **Fusion** proteins (**chimeric** proteins)
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(engineering and characterization of murine **MHC class II**-Ig chimera expressing immunodominant CD4 T viral epitope)

IT Immunoglobulin heavy chains
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(.gamma.2a-chain, **chimeric**; engineering and characterization of murine **MHC class II**-Ig chimera expressing immunodominant CD4 T viral epitope)

L2 ANSWER 46 OF 83 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 1998116887 MEDLINE
DOCUMENT NUMBER: 98116887 PubMed ID: 9455709
TITLE: Generation and characterization of a novel fusion partner cell line for the production of human macrophage hybridoma.
AUTHOR: Park J H; Cho E W; Lee Y J; Hahm K S; Kim K L
CORPORATE SOURCE: Peptide Engineering Research Unit, Korea Research Institute of Bioscience and Biotechnology (KRIBB), Taejon, Korea.
SOURCE: HYBRIDOMA, (1997 Dec) 16 (6) 551-6.
Journal code: GFS; 8202424. ISSN: 0272-457X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 19980312
Entered Medline: 19980302

AB Macrophages are important constituents of the immune system by exerting phagocytosis on invading pathogens as well as secreting various immunoregulatory factors. Generation of human macrophage hybridoma has not been possible so far due to the lack of an appropriate fusion partner cell line. In the present study, an 8'-azaguanine resistant cell line, termed HL-60R, was established by drug selection of the promyelocytic cell line HL-60. This novel cell line showed resistance to high concentrations of 8'-azaguanine and was sensitive to aminopterin. These characteristics make it suitable for serving as a potential fusion partner cell line in the development of macrophage hybridoma. Cell-surface analysis by FACS revealed that HL-60R cells per se do not express **MHC-class II** molecules or the macrophage marker, CD11b. PEG-mediated **fusion** of HL-60R was performed with PBMC-derived human macrophages. Fluorescence labelling of ex vivo isolated macrophages prior to fusion and subsequent FACS analysis showed that PEG-4000 is a more effective fusion agent than PEG-1500. The generation of this novel fusion partner cell line opens the possibility for development of human macrophage hybridoma or other cell lines from myelocytic origin. Such hybridoma clones will not only enable a more convenient study of these cell but will also provide an excellent host site for the proper production and expression of various recombinant proteins from myelocytic origin in vitro.

AB . . . line in the development of macrophage hybridoma. Cell-surface analysis by FACS revealed that HL-60R cells per se do not express **MHC-class II** molecules or the macrophage marker, CD11b. PEG-mediated **fusion** of HL-60R was performed with PBMC-derived human macrophages. Fluorescence labelling of ex vivo isolated macrophages prior to fusion and subsequent. . .

L2 ANSWER 47 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:419523 CAPLUS
DOCUMENT NUMBER: 129:188082
TITLE: Development and analysis of exotoxin A fusion proteins for the exogenous delivery of peptide antigens

AUTHOR(S): Galloway, D. R.; Denis[redacted] K. S.; Lippolis, J. D.; Engelhard, V. H.; Brinckerhoff, L. H.; Slingluff, C. L., Jr.
CORPORATE SOURCE: Department of Microbiology, The Ohio State University, Columbus, OH, 43210, USA
SOURCE: Zentralbl. Bakteriol., Suppl. (1997), 29(Bacterial Protein Toxins), 466-467
CODEN: ZBASE2; ISSN: 0941-018X
PUBLISHER: Gustav Fischer Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two model systems, representing both CD4+ and CD8+ T cell responses, have been employed to examine the efficacy of recombinant, non-cytotoxic Pseudomonas aeruginosa exotoxin A (PEI-II) for peptide delivery to either MHC class I or MHC class II processing pathways. The MHC class I model utilizes human cytotoxic T lymphocytes (CTLs) which recognize a melanoma-specific peptide (MEL-946). Using PEI-II with the MEL-946 fused in frame at the C-terminus (PE-946), the authors have demonstrated exogenous delivery of the nine residue melanoma-specific peptide to MHC class I mols. Chromium release assays for CTL activity confirmed that the that the PEI-II-MEL946 chimera stimulates an HLA A.2-restricted CTL response. A second model system was used to illustrate PEI-II-mediated delivery of peptides to MHC class II mols., using recombinant PEI-II protein linked to the proinsulin polypeptide (PEI-II-PI). The addn. of exogenous PEI-II-PI to antigen-presenting cells and insulin-specific murine CD4+ T cell clones results in IL-2 prodn. in vitro, indicative of T cell recognition of insulin epitopes in the context of MHC class II mols.

IT 9035-68-1, Proinsulin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(exotoxin A **fusion** protein for exogenous delivery to **MHC class II** processing pathway of CD4+ T-cell epitope of)

L2 ANSWER 48 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:710300 CAPLUS
DOCUMENT NUMBER: 127:357857
TITLE: Trophoblast and B-cell heterokaryons demonstrate lack of MHC class II expression
AUTHOR(S): Mandapati, Divakar; Coady, Michael A.; Al Ramadi, Basel; Bothwell, Alfred L. M.; Hammond, Graeme L.
CORPORATE SOURCE: Department of Surgery and Section of Immunobiology, Yale University School of Medicine, New Haven, CT, USA
SOURCE: Surg. Forum (1997), 48, 457-459
CODEN: SUFOAX; ISSN: 0071-8041
PUBLISHER: American College of Surgeons
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The outermost extravillous cytotrophoblast cells of the human placenta lack classical MHC complex mols. The authors have previously shown that HLA-DR.alpha., -DR.beta., and invariant chain synthesis of the MHC class II system is blocked at the transcriptional level in trophoblasts. As B-cells constitutively express MHC class II antigens, the authors examd. the result of trophoblast and B-cell fusion. In this report, **MHC class II** antigen expression is shown to be extinguished in transient **fusions** between the human class II-pos. B-cell line (UC) and the human trophoblast cell line (JAR). The results are compatible with the presence of suppressor factors of trophoblast origin that block MHC class II expression.

AB The outermost extravillous cytotrophoblast cells of the human placenta lack classical MHC complex mols. The authors have previously shown that HLA-DR.alpha., -DR.beta., and invariant chain synthesis of the MHC class II system is blocked at the transcriptional level in trophoblasts. As B-cells constitutively express MHC class II antigens, the authors examd. the result of trophoblast and B-cell fusion. In this report, **MHC class II** antigen expression is shown to be extinguished in transient **fusions** between the human class II-pos. B-cell line (UC) and the human trophoblast cell line (JAR). The results are compatible with the presence of suppressor factors of trophoblast origin that block MHC class II expression.

L2 ANSWER 49 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:476919 CAPLUS
DOCUMENT NUMBER: 125:132755
TITLE: Herpesvirus saimiri protein binding by **MHC class II** antigens, **fusion** proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders
INVENTOR(S): Yao, Zhengbin; Spriggs, Melanie; Alderson, Mark; Armitage, Richard
PATENT ASSIGNEE(S): Immunex Corporation, USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9617939	A1	19960613	WO 1995-US15948	19951207
W: AU, CA, FI, JP, KR, MX, NO, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5716623	A	19980210	US 1995-485549	19950606
AU 9644190	A1	19960626	AU 1996-44190	19951207

PRIORITY APPLN. INFO.: US 1994-351901 19941207
US 1995-485549 19950606
WO 1995-US15948 19951207

AB Isolated viral proteins, and compns. made therefrom, are disclosed which are capable of binding to class II major histocompatibility complex antigen, thereby functioning to inhibit an antigen-specific response. The isolated viral proteins also act as superantigens.

TI Herpesvirus saimiri protein binding by **MHC class II** antigens, **fusion** proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders

IT Antigens
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(antigen-specific immune response; herpesvirus saimiri protein binding by **MHC class II** antigens, **fusion** proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT Immunity
(antigen-specific; herpesvirus saimiri protein binding by **MHC**

class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT Allergy
Autoimmune disease
Immunosuppressants
Inflammation inhibitors
Protein sequences
(herpesvirus saimiri protein binding by MHC class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT Transplant and Transplantation
(rejection; herpesvirus saimiri protein binding by MHC class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT Histocompatibility antigens
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(MHC (major histocompatibility antigen complex), class II, herpesvirus saimiri protein binding by MHC class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(fusion products, Fc; herpesvirus saimiri protein binding by MHC class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT Virus, animal
(herpes saimiri, herpesvirus saimiri protein binding by MHC class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT Antigens
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(super-, herpesvirus saimiri protein binding by MHC class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT Organ
(transplant, herpesvirus saimiri protein binding by MHC class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT 133198-24-0, Phosphoprotein (herpes saimiri virus clone pHindIII-G 52.0-kilodalton reduced) 179671-94-4 179671-95-5D, Immunoglobulin G1 (human Fc region), fusion products with HSV14 protein
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(amino acid sequence; herpesvirus saimiri protein binding by MHC class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT 172724-59-3D, fusion products with HSV14 protein
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(dimeric oligomerization zipper, amino acid sequence; herpesvirus saimiri protein binding by MHC class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

IT 157214-04-5D, fusion products with HSV14 protein
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(trimeric oligomerization zipper, amino acid sequence; herpesvirus saimiri protein binding by MHC class II antigens, fusion proteins, amino acid sequences, and therapeutic uses in treating antigen-specific immune disorders)

L2 ANSWER 50 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:48657 CAPLUS
DOCUMENT NUMBER: 126:73775
TITLE: Immobilized MHC class II fusion protein for removal or detection of superantigen
INVENTOR(S): Miwa, Takashi; Fukuyama, Mayumi; Ishikawa, Kazuo
PATENT ASSIGNEE(S): Toray Industries, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 08283300	A2	19961029	JP 1995-89494	19950414

AB The disclosed fusion proteins comprise a partial sequence of MHC class II .alpha. subunit, a spacer peptide and a partial sequence of .beta. subunit of MHC class II. The fusion protein has high affinity for superantigen and reserves T cell activation activity. The fusion protein is coated on carrier (e.g. natural or synthetic polymer) for removal or sepn. of superantigen, e.g. toxic shock syndrome toxin-1.

TI Immobilized MHC class II fusion protein for removal or detection of superantigen

AB The disclosed fusion proteins comprise a partial sequence of MHC class II .alpha. subunit, a spacer peptide and a partial sequence of .beta. subunit of MHC class II. The fusion protein has high affinity for superantigen and reserves T cell activation activity. The fusion protein is coated on carrier (e.g. natural or synthetic polymer) for removal or sepn. of superantigen, e.g. toxic shock syndrome toxin-1.

ST MHC class II fusion protein superantigen

IT Class II MHC antigens

Fusion proteins (**chimeric** proteins)
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
(carrier-immobilized **fusion** protein of **MHC class II** for removal or detection of superantigen)

IT Carriers
T-cell activation
(natural or synthetic polymer-immobilized **fusion** protein of **MHC class II** for removal or detection of superantigen)

IT Superantigens
Toxic shock syndrome toxin 1
RL: ANT (Analyte); PUR (Purification or recovery); REM (Removal or disposal); ANST (Analytical study); PREP (Preparation); PROC (Process)
(natural or synthetic polymer-immobilized **fusion** protein of **MHC class II** for removal or detection of superantigen)

L2 ANSWER 51 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:725480 CAPLUS
DOCUMENT NUMBER: 126:17755
TITLE: Single-chain MHC class II molecules induce T cell activation and apoptosis
AUTHOR(S): Rhode, Peter R.; Burkhardt, Martin; Jiao, Jin-an; Siddiqui, Ayesha H.; Huang, Grace P.; Wong, Hing C.
CORPORATE SOURCE: Sunol Molecular Corporation, Miami, FL, 33172, USA
SOURCE: J. Immunol. (1996), 157(11), 4885-4891
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB MHC class II/peptide complexes displayed on the surface of APCs play a pivotal role in initiating specific T cell responses. Evidence is presented here that components of this heterotrimeric complex can be genetically linked into a single polypeptide chain. Sol. single-chain (s.c.) murine class II IAd mols. with and without covalently attached peptides were produced in a recombinant baculovirus-insect cell expression system. Correct conformation of these mols. was verified based on (1) reactivity to Abs directed against conformational epitopes in IAd and (2) peptide-specific recognition of the IAd/peptide complexes by T cells. Both s.c. class II mols. loaded the appropriate peptides and s.c. class Ii/peptide fusions were effective in stimulating T cell responses, including cytokine release and apoptosis. Mammalian cells were also capable of expressing functional s.c. class II mols. on their cell surfaces. These findings open up the possibility of producing large amts. of stable s.c. class II/peptide fusion mols. for structural characterization and immunotherapeutic applications.

IT DNA sequences
Protein sequences
(of single-chain **MHC class II**-peptide **fusion** mol.)

L2 ANSWER 52 OF 83 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 97051784 MEDLINE
DOCUMENT NUMBER: 97051784 PubMed ID: 8896419
TITLE: Recognition of BCR-ABL positive leukemic blasts by human CD4+ T cells elicited by primary in vitro immunization with a BCR-ABL breakpoint peptide.
AUTHOR: Bosch G J; Joosten A M; Kessler J H; Melief C J; Leeksma O C
CORPORATE SOURCE: Department of Immunohaematology and Bloodbank, Leiden University Hospital, The Netherlands.
SOURCE: BLOOD, (1996 Nov 1) 88 (9) 3522-7.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961216

AB In chronic myeloid leukemia (CML) the classical 9;22 translocation results in a BCR-ABL fusion gene, which encodes chimeric BCR-ABL fusion 210 kD oncoproteins (p210BCR-ABL). The two main p210BCR-ABL fusion variants in CML, b2a2 and b3a2 are examples of well characterized antigens expressed by malignant cells. The possibility of an immunotherapeutic approach involving the fusion part of p210BCR-ABL in CML has previously been illustrated by observed peptide binding to major histocompatibility complex (MHC) class I alleles and by demonstrating the immunogenicity of p210BCR-ABL breakpoint peptides. In this report we show that in vitro immunization of human T cells with a 17 amino acid (aa) peptide representing the p210BCR-ABL fusion region resulted in peptide specific CD4+ T-cell lines designated P4, P6, and P7. HLA DR4 (DRB1*0401) restricted T-cell line P4 and several subsequently derived clones recognized HLA-DRB1*0401 and p210b3a2-mRNA expressing blasts from an allogeneic patient with CML in blast crisis. Recognition appeared DR expression-dependent. No responses were observed with DR4 positive p210BCR-ABL negative cells or with p210b3a2 leukemic cells with absent or insufficient expression of DR4. These observations indicate that oncoprotein p210b3a2 can be degraded and processed for presentation by **MHC class II** molecules at the surface of leukemic cells. The BCR-ABL **fusion** region is in all likelihood presented as peptides by HLA DR and thus capable to act as a distinctive tumor antigen to peptide specific CD4+ T cells.

AB . . . absent or insufficient expression of DR4. These observations indicate that oncoprotein p210b3a2 can be degraded and processed for presentation by **MHC class II** molecules at the surface of leukemic cells. The BCR-ABL **fusion** region is in all likelihood presented as peptides by HLA DR and thus capable to act as a distinctive tumor. . .

L2 ANSWER 53 OF 83 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 96194531 MEDLINE
DOCUMENT NUMBER: 96194531 PubMed ID: 8617948
TITLE: Herpesvirus saimiri open reading frame 14, a protein encoded by T lymphotropic herpesvirus, binds to MHC class II molecules and stimulates T cell proliferation.
AUTHOR: Yao Z; Maraskovsky E; Spriggs M K; Cohen J I; Armitage R J; Alderson M R
CORPORATE SOURCE: Immunex Corporation, Seattle, WA 98101, USA.
SOURCE: JOURNAL OF IMMUNOLOGY, (1996 May 1) 156 (9) 3260-6.
Journal code: IFB; 2985117R. ISSN: 0022-1767.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960620
Last Updated on STN: 19970203
Entered Medline: 19960613

AB Herpesvirus saimiri (HVS) is an oncogenic, lymphotropic, gamma-herpesvirus that transforms human and simian T cells in vitro and causes lymphomas and leukemias in various species of New World primates. Nucleotide sequence analysis of the HVS genome revealed an open reading frame with 22% amino acid identity to the mouse mammary tumor virus 7 superantigen. In this study, we demonstrate that this open reading frame, HVS14, encodes a heavily glycosylated protein that is secreted. Both the HVS14 present in the supernatant of transfected cells and a **chimeric** HVS14.Fc **fusion** protein were found to bind to heterodimeric **MHC class II** HLA-DR molecules. The supernatant from HVS14-transfected cells induced the proliferation of human PBMC, which could be specifically inhibited by HVS14-specific mAbs. Purified peripheral blood T cells were induced to proliferate in the presence of accessory cells and HVS14-containing supernatant. Whereas the HVS14 protein stimulated T cell proliferation, the HVS14.Fc fusion protein blocked proliferative responses to soluble Ags in vitro. Collectively, these data indicate that HVS14 can function as an immunomodulator that may contribute to the immunopathology of HVS infection.

AB . . . encodes a heavily glycosylated protein that is secreted. Both the HVS14 present in the supernatant of transfected cells and a **chimeric** HVS14.Fc **fusion** protein were found to bind to heterodimeric **MHC class** II HLA-DR molecules.
The supernatant from HVS14-transfected cells induced the proliferation of human PBMC, which could be specifically inhibited by HVS14-specific. . .

L2 ANSWER 54 OF 83 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 96164573 MEDLINE
DOCUMENT NUMBER: 96164573 PubMed ID: 8568247
TITLE: A zinc finger protein that represses transcription of the human MHC class II gene, DPA.
AUTHOR: Scholl T; Stevens M B; Mahanta S; Strominger J L
CORPORATE SOURCE: Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA 02138, USA.
CONTRACT NUMBER: CA47554 (NCI)
DK32041 (NIDDK)
SOURCE: JOURNAL OF IMMUNOLOGY, (1996 Feb 15) 156 (4) 1448-57.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
OTHER SOURCE: GENBANK-U22680
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960315
Last Updated on STN: 19960315
Entered Medline: 19960306

AB The proximal promoters of all MHC class II genes contain a sequence element, the 19-bp X box, that is conserved in both sequence and position. Extensive analysis using a wide variety of approaches has demonstrated that the integrity of the X box is essential for transcription initiation from all class II genes studied. However, the X box is now recognized to contain two subregions, termed X1 and X2. Radiolabeled oligonucleotides corresponding to the X2 box of the MHC class II genes DPA and DQB were used to screen B cell and T cell expression libraries. A novel cDNA, termed XBR (X box repressor), encoding a putative zinc finger protein that binds specifically to the DPA X2 box was isolated from a human T cell line. The XBR gene encodes a 7-kb message that is ubiquitously transcribed, although at higher levels in tissues of the lymphocytic compartment. Southern blots indicate that this gene is single copy in primates and contains regions that are highly divergent in other species. Overexpression of XBR in a B cell line resulted in a dramatic reduction of transcription from a reporter gene construct driven by the DPA promoter, but not from similar constructs with mutations in the X2 box. Similarly, overexpression of XBR reduced induction of reporter gene activity driven from the DPA promoter in HeLa cells treated with IFN-gamma. XBR may, therefore, mediate transcriptional repression, thus preventing inappropriate MHC class II expression. XBR function may in part explain the dominant trans-acting repression of **MHC class II** expression reported in cell **fusion** experiments.

AB . . . transcriptional repression, thus preventing inappropriate MHC class II expression. XBR function may in part explain the dominant trans-acting repression of **MHC class II** expression reported in cell **fusion** experiments.

L2 ANSWER 55 OF 83 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 96298727 MEDLINE
DOCUMENT NUMBER: 96298727 PubMed ID: 8671631
TITLE: Activation of T cells by the ragged tail of **MHC class II**-presented peptides of the measles virus **fusion** protein.
AUTHOR: Muller C P; Ammerlaan W; Fleckenstein B; Krauss S; Kalbacher H; Schneider F; Jung G; Wiesmuller K H
CORPORATE SOURCE: Laboratoire National de Sante, Luxembourg, Germany.
SOURCE: INTERNATIONAL IMMUNOLOGY, (1996 Apr) 8 (4) 445-56.
Journal code: AY5; 8916182. ISSN: 0953-8178.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961125

AB The efficient and sustained immune response of an antigen requires T cell epitopes, capable of inducing a long lasting T cell memory. To detect T cell epitopes of the measles virus fusion protein (MV-F), the proliferation of lymphocytes from late convalescent donors in response to overlapping pentadecapeptides covering the whole protein sequence was studied. Three major immunodominant regions (F51-70, F121-135 and F211-225) containing promiscuous peptides induce proliferation in peripheral blood lymphocytes in approximately 50% of the donors. Potential DR1-restricted epitopes were mapped using an MHC competition binding assay. Both the proliferation and the binding data identified a DR1-restricted T cell epitope (F51-65). Contact sites of the peptide HQSLVIKLMPNITLL with MHC were characterized using substitution analogs.

Alanine substitutions at most positions did not interfere with F51-65 binding. These analogs were therefore useful for studying the residues which were recognized by the TCR of MV- and F51-induced T cells lines. In addition to amino acid residues of the core of peptide F51-65 both the C-terminal and the N-terminal amino acids were essential for T cell interaction. Since peptides presented by class II molecules vary in length, these findings suggest that residues of the ragged tail are important for T cell activation. It is speculated that in late convalescent donors the length of the flanking sequence of MHC II-restricted peptides may play a role in controlling the heterogeneity of MV-specific T cell clones recruited as T helper/memory cells.

TI Activation of T cells by the ragged tail of **MHC class** II-presented peptides of the measles virus **fusion** protein.

L2 ANSWER 56 OF 83 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 97081031 MEDLINE
DOCUMENT NUMBER: 97081031 PubMed ID: 8964079
TITLE: Homogeneous processing and presentation of a recombined T cell epitope in inbred mice of different non-MHC genetic background.
AUTHOR: Lo-Man R; Martineau P; Hofnung M; Leclerc C
CORPORATE SOURCE: Unite de Biologie des Regulations Immunitaires, Institut Pasteur, Paris, France.
SOURCE: CELLULAR IMMUNOLOGY, (1996 Sep 15) 172 (2) 180-91. Journal code: CQ9; 1246405. ISSN: 0008-8749.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961203

AB CD4+ T cell responses are restricted by **MHC class** II-encoded glycoproteins which display antigen-derived peptides. **Chimeric** MalE proteins expressing foreign T cell epitopes represent a potent means to induce immune responses for recombinant vaccine design. Here, we studied the influence of the non-MHC genetic background and of the processing heterogeneity displayed by various APC types on the presentation of these chimeric proteins to T cells. For this purpose, the I-Ed-restricted poliovirus CD4+ T cell epitope was inserted into five different positions on the surface of MalE protein and the immunogenicity of the recombined T cell epitope was determined in different inbred mice. Immunization of several mouse strains expressing I-Ed with these chimeric proteins induced poliovirus-specific T cell response with four out of five constructs. In vitro presentation studies of the recombined epitope to specific T cells indicated that for a given chimeric protein the fine processing is conserved, whatever the non-H-2 genetic background of APC or the type of APC. Our results show that the insertion site in MalE modulates the immunogenicity of the recombined T cell epitope, but this phenomenon is only related to the MHC genetic background.

AB CD4+ T cell responses are restricted by **MHC class** II-encoded glycoproteins which display antigen-derived peptides. **Chimeric** MalE proteins expressing foreign T cell epitopes represent a potent means to induce immune responses for recombinant vaccine design. Here,. . .

L2 ANSWER 57 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:34810 CAPLUS
DOCUMENT NUMBER: 124:84899
TITLE: Chimeric polypeptide for improvement of peptide delivery
INVENTOR(S): Cardy, Donald Leonard Nicholas; Carr, Frank Joseph
PATENT ASSIGNEE(S): Eclagen Ltd., UK
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9531483	A1	19951123	WO 1995-GB1107	19950515
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2190101	AA	19951123	CA 1995-2190101	19950515
AU 9524521	A1	19951205	AU 1995-24521	19950515
AU 701302	B2	19990121		
EP 759944	A1	19970305	EP 1995-918692	19950515
R: AT, BE, CH, DE, DK, ES, FR, GB, IE, IT, LI, NL, SE				
JP 10500670	T2	19980120	JP 1995-529465	19950515

PRIORITY APPLN. INFO.: GB 1994-9643 A 19940513
GB 1994-17461 A 19940831
WO 1995-GB1107 W 19950515

AB Disclosed is a chimeric polypeptide comprising: a binding portion having specific binding affinity for a eukaryotic target cell surface component and an effector portion comprising an amino acid sequence capable of exerting a biol. effect. Binding of the polypeptide to the cell surface component induces internalization of at least the effector portion so as to allow the amino acid sequence to exert its biol. effect. A vaccine comprising the chimeric polypeptide of the invention, and a method of modulating the immune response of a human or animal subject are also included. In example, **chimeric** polypeptide contg. anti-**MHC class II** peptide and p53 or influenza A matrix protein peptide was prepd. and tested for cell lysis induction. Recombinant antibody specific for MBr1 antigen and p53 or influenza A matrix protein was also prepd. to induce cytotoxic T lymphocyte activity against MCF7 cells.

AB Disclosed is a chimeric polypeptide comprising: a binding portion having specific binding affinity for a eukaryotic target cell surface component and an effector portion comprising an amino acid sequence capable of exerting a biol. effect. Binding of the polypeptide to the cell surface component induces internalization of at least the effector portion so as to allow the amino acid sequence to exert its biol. effect. A vaccine comprising the chimeric polypeptide of the invention, and a method of

modulating the immune response of a human or animal subject are also included. In example, **chimeric** polypeptide contg. anti-**MHC class II** peptide and p53 or influenza A matrix protein peptide was prepd. and tested for cell lysis induction. Recombinant antibody specific for MBr1 antigen and p53 or influenza A matrix protein was also prepd. to induce cytotoxic T lymphocyte activity against MCF7 cells.

L2 ANSWER 58 OF 83 MEDLINE DUPLICATE 23
ACCESSION NUMBER: 95365339 MEDLINE
DOCUMENT NUMBER: 95365339 PubMed ID: 7638170
TITLE: Expression of endogenous peptide-major histocompatibility complex class II complexes derived from invariant chain-antigen fusion proteins.
AUTHOR: Sanderson S; Frauwirth K; Shastri N
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California, Berkeley 94720, USA.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Aug 1) 92 (16) 7217-21. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950921
Last Updated on STN: 19950921
Entered Medline: 19950911

AB CD4+ T cells recognize major histocompatibility complex (MHC) class II-bound peptides that are primarily obtained from extracellular sources. Endogenously synthesized proteins that readily enter the MHC class I presentation pathway are generally excluded from the MHC class II presentation pathway. We show here that endogenously synthesized ovalbumin or hen egg lysozyme can be efficiently presented as peptide-**MHC class II** complexes when they are expressed as **fusion** proteins with the invariant chain (Ii). Similar to the wild-type Ii, the Ii-antigen fusion proteins were associated intracellularly with MHC molecules. Most efficient expression of endogenous peptide-MHC complex was obtained with fusion proteins that contained the endosomal targeting signal within the N-terminal cytoplasmic Ii residues but did not require the luminal residues of Ii that are known to bind MHC molecules. These results suggest that signals within the Ii can allow endogenously synthesized proteins to efficiently enter the MHC class II presentation pathway. They also suggest a strategy for identifying unknown antigens presented by MHC class II molecules.

AB . . . class II presentation pathway. We show here that endogenously synthesized ovalbumin or hen egg lysozyme can be efficiently presented as peptide-**MHC class II** complexes when they are expressed as **fusion** proteins with the invariant chain (Ii). Similar to the wild-type Ii, the Ii-antigen fusion proteins were associated intracellularly with MHC. . .

L2 ANSWER 59 OF 83 MEDLINE DUPLICATE 24
ACCESSION NUMBER: 96011893 MEDLINE
DOCUMENT NUMBER: 96011893 PubMed ID: 7589152
TITLE: CD4/major histocompatibility complex class II interaction analyzed with CD4- and lymphocyte activation gene-3 (LAG-3)-Ig fusion proteins.
AUTHOR: Huard B; Prigent P; Tournier M; Bruniquel D; Triebel F
CORPORATE SOURCE: Laboratoire d'Immunologie Cellulaire, INSERM U333, Institut Gustave-Roussy, Villejuif, France.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Sep) 25 (9) 2718-21. Journal code: EN5; 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951128

AB We analyzed CD4 major histocompatibility complex (**MHC**) **class II** interactions with CD4 and lymphocyte activation gene (LAG)-3 recombinant **fusion** proteins termed CD4Ig and LAG-3Ig. CD4Ig bound **MHC class II** molecules expressed on the cell surface only when used in the micromolar range. This weak CD4Ig binding was specific, since it was inhibited by anti-CD4 and anti-MHC class II mAb. LAG-3Ig bound MHC class II molecules with intermediate avidity (Kd ≈ 60 nM at 37 degrees C). Using LAG-3Ig as a competitor in a CD4/MHC class II-dependent cellular adhesion assay, we showed that this recombinant molecule was able to block CD4/MHC class II interaction. In contrast, no inhibition was observed in a CD4/MHC class II-dependent T cell cytotoxicity assay. Together, these results suggest that co-engagement of the TcR with CD4 alters the CD4/MHC class II molecular interaction to become insensitive to LAG-3Ig competition.

AB We analyzed CD4 major histocompatibility complex (**MHC**) **class II** interactions with CD4 and lymphocyte activation gene (LAG)-3 recombinant **fusion** proteins termed CD4Ig and LAG-3Ig. CD4Ig bound **MHC class II** molecules expressed on the cell surface only when used in the micromolar range. This weak CD4Ig binding was specific since. . .

L2 ANSWER 60 OF 83 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 95387666 MEDLINE
DOCUMENT NUMBER: 95387666 PubMed ID: 7544852
TITLE: Antibodies are capable of directing superantigen-mediated T cell killing of chronic B lymphocytic leukemia cells.
AUTHOR: Gidlof C; Dohlsten M; Kalland T; Totterman T H
CORPORATE SOURCE: Department of Clinical Immunology, University Hospital, Uppsala, Sweden.
SOURCE: LEUKEMIA, (1995 Sep) 9 (9) 1534-42. Journal code: LEU; 8704895. ISSN: 0887-6924.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951013
Last Updated on STN: 19970203
Entered Medline: 19951005

AB The bacterial superantigen staphylococcal enterotoxin A (SEA) is a highly potent activator of cytotoxic T cells when presented on MHC class II molecules of target cells. Our earlier studies showed that such

SEA-directed T cells efficiently killed chronic B lymphocytic leukemia (B-CLL) cells. With the ultimate goal to replace the natural specificity of SEA for MHC class II molecules with the specificity of a monoclonal antibody (mAb), we initially made a mutated protein A-SEA (PA-SEAm) **fusion** protein with > 100-fold reduced binding affinity for **MHC class II** compared to native SEA. The **fusion** protein was successfully used to direct T cells to B-CLL cells coated with different B lineage specific (CD19, CD20) or associated (CD37, CD40) mAbs. The PA-SEAm protein was 10-100-fold more potent against mAb coated compared to uncoated HLA class II+ B-CLL cells. No correlation was seen between the amount of mAb bound to the cell surface and sensitivity to lysis. Preactivation of B-CLL cells by phorbol ester increased their sensitivity, and lysis was dependent on ICAM-1 molecules. However, no preactivation of the target cells was needed when a cocktail of two or four mAbs was used. Circulating leukemia and spleen cells were equally well killed. We conclude that the natural target specificity of SEA, MHC class II, can be reduced by mutagenesis and novel binding specificity can be introduced by linkage to tumor reactive mAbs. Our findings encourage the construction of recombinant SEA mutant fusion proteins for specific T cell therapy of hematopoietic tumors such as B-CLL.

AB . . . MHC class II molecules with the specificity of a monoclonal antibody (mAb), we initially made a mutated protein A-SEA (PA-SEAm) **fusion** protein with > 100-fold reduced binding affinity for **MHC class II** compared to native SEA. The **fusion** protein was successfully used to direct T cells to B-CLL cells coated with different B lineage specific (CD19, CD20) or. . .

L2 ANSWER 61 OF 83 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:385872 BIOSIS
DOCUMENT NUMBER: PREV199598400172
TITLE: Antibody targeted sea mutant **fusion** protein display reduced **MHC class II** binding and toxicity, but retains anti-tumor effects in vivo.
AUTHOR(S): Dohlsten, M.. (1); Hansson, J.; Bjork, P.; Kalland, T.
CORPORATE SOURCE: (1) Pharmacia Oncol. Immunol., Lund Sweden
SOURCE: 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 890. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995
DOCUMENT TYPE: Conference
LANGUAGE: English
TI Antibody targeted sea mutant **fusion** protein display reduced **MHC class II** binding and toxicity, but retains anti-tumor effects in vivo.

L2 ANSWER 62 OF 83 MEDLINE DUPLICATE 26
ACCESSION NUMBER: 95136241 MEDLINE
DOCUMENT NUMBER: 95136241 PubMed ID: 7530598
TITLE: Antibody-targeted superantigens induce lysis of major histocompatibility complex class II-negative T-cell leukemia lines.
AUTHOR: Ihle J; Holzer U; Krull F; Dohlsten M; Kalland T; Niethammer D; Dannecker G E
CORPORATE SOURCE: Department of Oncology/Hematology, Children's University Hospital, Tubingen, Germany.
SOURCE: CANCER RESEARCH, (1995 Feb 1) 55 (3) 623-8. Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950314
Last Updated on STN: 19990129
Entered Medline: 19950228
AB CTLs bearing certain T-cell receptor V beta-regions are directed by the bacterial superantigen Staphylococcus enterotoxin A (SEA) to lyse MHC class II-positive cells. In order to extend superantigen-dependent cytotoxicity to MHC class II-negative carcinoma cells, covalent conjugates of superantigen and mAbs against surface markers of these cells have been used. We now describe a novel strategy which allows rapid selection of mAb suitable for superantigen targeting against **MHC class II**-negative tumor cells. A recombinant **fusion** protein of protein A and SEA binding to the mAbs CD7 or CD38 was able to mediate T cell-dependent lysis of MHC class II-negative Molt-4 and CCRF-CEM acute lymphatic leukemia cell lines. Lysis was dose dependent and correlated with E:T cell ratio. In contrast, SEA alone did not induce any significant lysis. In order to decrease the MHC class II affinity of the protein A-SEA complex, a point mutation was introduced into SEA (protein A-SEA mu9). The mutated fusion protein had similar potency as protein A-SEA against Molt-4 cells but was 100-fold less active against MHC class II-positive cells. Considering the efficiency and specificity of the mutated SEA protein interacting with mAb in targeting T lymphocytes against MHC class II-negative leukemia cells while only marginally affecting normal **MHC class II**-positive cells, we suggest the development of SEA-mAb **fusion** proteins as a potential adjuvant therapy of leukemias.
AB . . . have been used. We now describe a novel strategy which allows rapid selection of mAb suitable for superantigen targeting against **MHC class II**-negative tumor cells. A recombinant **fusion** protein of protein A and SEA binding to the mAbs CD7 or CD38 was able to mediate T cell-dependent lysis. . . SEA protein interacting with mAb in targeting T lymphocytes against MHC class II-negative leukemia cells while only marginally affecting normal **MHC class II**-positive cells, we suggest the development of SEA-mAb **fusion** proteins as a potential adjuvant therapy of leukemias.

L2 ANSWER 63 OF 83 MEDLINE DUPLICATE 27
ACCESSION NUMBER: 95270291 MEDLINE
DOCUMENT NUMBER: 95270291 PubMed ID: 7751017
TITLE: Genetic restriction and specificity of the immune response in mice to fusion proteins containing repeated sequences of the Plasmodium falciparum antigen Pf155/RESA.
AUTHOR: Sjolander A; Andersson R; Hansson M; Berzins K; Perlmann P
CORPORATE SOURCE: Department of Immunology, Stockholm University, Sweden.
SOURCE: IMMUNOLOGY, (1995 Mar) 84 (3) 360-6.

Journal code: GH7; 0374672. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950629
Last Updated on STN: 19980206
Entered Medline: 19950619

AB The genetic restriction and specificity of the immune response in mice to two fusion proteins, ZZ-M3 and ZZ-M5, were studied. These proteins contain two IgG-binding domains (ZZ) from staphylococcal protein A, and repeated sequences from the C-terminal [(VEHDAEEN)5 (VEEN)10] (M3) or central [(VEEPTVADDEH)3(VEEPTVAEEH)2] (M5) regions of the Plasmodium falciparum malaria blood stage antigen Pf155/RESA. Strong antibody and T-cell responses to M3 and M5 were linked to expression of the I-Ak allele, and T-cell responses to the bacterial fusion partner ZZ were restricted to mice of the H-2k haplotype. The response to M5 was less restricted than that to M3, giving intermediate responses in mice of H-2d haplotypes as well. However, ZZ-M5-primed lymph node (LN) cells from these mice were primarily induced to proliferate in vitro by the complete ZZ-M5 construct and not by synthetic peptides representing the repeated subunits in M5. The reactivity with intact Pf155/RESA in erythrocyte membrane immunofluorescence was weak of antisera from mice immunized with ZZ-M5, whereas the reactivity of antisera from mice immunized with ZZ-M3 roughly paralleled their reactivity with M3 in an enzyme-linked immunosorbent assay (ELISA). The antibody responses induced by immunization with ZZ-M3 or ZZ-M5 were specific for M3 or M5, respectively, while activated T cells displayed cross-reactivity between M3 and M5 in an in vitro proliferation assay. The results indicate that the assembly of repeated sequences in **fusion** proteins affects both the **MHC class** II restriction and the specificity of the-induced antibody and T-cell responses.

AB . . . between M3 and M5 in an in vitro proliferation assay. The results indicate that the assembly of repeated sequences in **fusion** proteins affects both the **MHC class II** restriction and the specificity of the induced antibody and T-cell responses.

L2 ANSWER 64 OF 83 MEDLINE DUPLICATE 28
ACCESSION NUMBER: 96001370 MEDLINE
DOCUMENT NUMBER: 96001370 PubMed ID: 7553685
TITLE: Immunotherapy of human colon cancer by antibody-targeted superantigens.
AUTHOR: Dohlsten M; Lando P A; Bjork P; Abrahmsen L; Ohlsson L; Lind P; Kalland T
CORPORATE SOURCE: Pharmacia AB, Lund, Sweden.
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1995 Sep) 41 (3) 162-8.
Journal code: CN3; 8605732. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951024

AB T lymphocytes generally fail to recognize human colon carcinomas, suggesting that the tumour is beyond reach of immunotherapy. Bacterial superantigens are the most potent known activators of human T lymphocytes and induce T cell cytotoxicity and cytokine production. In order to develop a T-cell-based therapy for colon cancer, the superantigen staphylococcal enterotoxin A (SEA) was given tumour reactivity by genetic fusion with a Fab fragment of the monoclonal antibody C242 reacting with human colon carcinomas. The C242Fab-SEA **fusion** protein targeted SEA-reactive T cells against **MHC-class-II** -negative human colon carcinoma cells in vitro at nanomolar concentrations. Treatment of disseminated human colon carcinomas growing in humanized SCID mice resulted in marked inhibition of tumour growth and the apparent cure of the animals. Therapeutic efficiency was dependent on the tumour specificity of the fusion protein and human T cells. Immunohistochemistry demonstrated massive infiltration of human T cells in C242Fab-SEA-treated tumours. The results merit further evaluation of C242Fab-SEA fusion proteins as immunotherapy in patients suffering from colon carcinoma.

AB . . . reactivity by genetic fusion with a Fab fragment of the monoclonal antibody C242 reacting with human colon carcinomas. The C242Fab-SEA **fusion** protein targeted SEA-reactive T cells against **MHC-class-II**-negative human colon carcinoma cells in vitro at nanomolar concentrations. Treatment of disseminated human colon carcinomas growing in humanized SCID mice. . .

L2 ANSWER 65 OF 83 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 95237891 MEDLINE
DOCUMENT NUMBER: 95237891 PubMed ID: 7721346
TITLE: Class II cytoplasmic and transmembrane domains are not required for class II-mediated B cell spreading.
AUTHOR: Wade W F; Dickman D K; Peterson D; McCluskey J; Khrebtukova I
CORPORATE SOURCE: School of Biological Science, University of Nebraska-Lincoln, Lincoln 68588-0118, USA.
CONTRACT NUMBER: AI31160 (NIAID)
CA58772 (NCI)
SOURCE: IMMUNOLOGY LETTERS, (1995 Jan) 44 (1) 67-74.
Journal code: GIM; 7910006. ISSN: 0165-2478.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950605
Last Updated on STN: 19970203
Entered Medline: 19950525

AB B cells cultured on immobilized anti-class II monoclonal antibody (mAb) change from round to flattened cells, with lamellipodia and filopodia. This change in cell morphology, termed 'spiders', occurs within 30 min upon culture and is mediated through either I-A or I-E molecules. Class II molecules that are defective in mediating protein kinase C (PKC) due to the deletions of both alpha and beta chain's cytoplasmic (Cy) domain sequences can induce spider formation. B-cell transfectants that express **chimeric MHC class** II/class I molecules, where the ectodomains are class II sequences and the transmembrane and Cy domains are class I sequences also form spiders when

cultured on anti-class II mAb. The spider morphology is not induced by either anti-immunoglobulin (Ig) or anti-MHC class I mAb. Treatment of B cells to increase intracellular cAMP, a component of the class II signaling pathway also results in spider formation with the same kinetics and percent change in the responding population as that induced by anti-class II mAb. Cytochalasin A treatment which disrupts cytoskeletal actin filaments and the tyrosine kinase inhibitor, genistein, both inhibit spider formation. Actin redistributes from a concentric ring in round cells to the ends of the filopodia in the spiders. The mechanism of spider induction whether resultant from second messengers following class II signaling or from non-signaling-induced physical interactions of class II with intracellular cytoskeletal components only requires the extracellular domains of class II. The biologic relevance of B-cell spiders is currently not known but has been reported to be associated with class II signal transduction and efficient Ag presentation.

AB . . . the deletions of both alpha and beta chain's cytoplasmic (Cy) domain sequences can induce spider formation. B-cell transfectants that express **chimeric MHC class II** /class I molecules, where the ectodomains are class II sequences and the transmembrane and Cy domains are class I sequences also. . .

L2 ANSWER 66 OF 83 MEDLINE DUPLICATE 30
ACCESSION NUMBER: 95338610 MEDLINE
DOCUMENT NUMBER: 95338610 PubMed ID: 7613876
TITLE: Molecular structure and function of CD4 on murine egg plasma membrane.
AUTHOR: Guo M W; Watanabe T; Mori E; Mori T
CORPORATE SOURCE: Department of Immunology and Pathology, University of Tokyo, Japan.
SOURCE: ZYGOTE, (1995 Feb) 3 (1) 65-73.
Journal code: B33; 9309124. ISSN: 0967-1994.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950905
Last Updated on STN: 19960129
Entered Medline: 19950824

AB In the present study, the expression of the CD4 molecule on murine egg plasma membrane was confirmed by the indirect immunofluorescence (IIF) method. The full-length CD4 cDNA from murine eggs was synthesised by the reverse transcriptase-polymerase chain reaction (RT-PCR) method and its authenticity verified by Southern blot hybridisation using an end-labelled internal oligonucleotide. The results of DNA sequencing showed that the nucleotide sequence of the cDNA of CD4 from murine egg mRNA was identical to that of immune T cells. To demonstrate the direct interaction of CD4 from murine egg with murine sperm cells bearing MHC (major histocompatibility complex) class II molecule, we employed a baculovirus expression system to generate CD4 on the surface of Spodoptera frugiperda (Sf9) cells. Expression of CD4 on Sf9 cells infected with Autographa californica nuclear polyhedrosis virus (AcNPV)-CD4 was demonstrated by IIF and immunoblotting. The CD4-expressing Sf9 cells adhered to MHC class II-bearing sperm cells since the adhesion was specifically blocked by anti-CD4 monoclonal antibody (mAb) or anti-monomorphic region of MHC class II mAb. Taking our previous and present experimental results together, they strongly suggest that intercellular membrane adhesion between two gametes at the **fusion** step in fertilisation is mediated by the **MHC class II** molecule located on the posterior region of the sperm head and the CD4 molecule on egg plasma membrane.

AB . . . Taking our previous and present experimental results together, they strongly suggest that intercellular membrane adhesion between two gametes at the **fusion** step in fertilisation is mediated by the **MHC class II** molecule located on the posterior region of the sperm head and the CD4 molecule on egg plasma membrane.

L2 ANSWER 67 OF 83 MEDLINE DUPLICATE 31
ACCESSION NUMBER: 94377469 MEDLINE
DOCUMENT NUMBER: 94377469 PubMed ID: 8090750
TITLE: Monoclonal antibody-superantigen fusion proteins: tumor-specific agents for T-cell-based tumor therapy.
AUTHOR: Dohlsten M; Abrahmsen L; Bjork P; Lando P A; Hedlund G; Forsberg G; Brodin T; Gascoigne N R; Forberg C; Lind P; +
CORPORATE SOURCE: Wallenberg Laboratory, Department of Tumor Immunology, University of Lund, Sweden.
CONTRACT NUMBER: GM46134 (NIGMS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Sep 13) 91 (19) 8945-9.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941031
Last Updated on STN: 19941031
Entered Medline: 19941014

AB The bacterial superantigen staphylococcal enterotoxin A (SEA) is an extremely potent activator of T lymphocytes when presented on major histocompatibility complex (MHC) class II molecules. To develop a tumor-specific superantigen for cancer therapy, we have made a recombinant fusion protein of SEA and the Fab region of the C215 monoclonal antibody specific for human colon carcinoma cells. SEA as part of a **fusion** protein showed a > 10-fold reduction in **MHC class II** binding compared to native SEA, and accordingly, the affinity of the FabC215-SEA fusion protein for the C215 tumor antigen was approximately 100-fold stronger than to **MHC class II** molecules. The FabC215-SEA **fusion** protein efficiently targeted T cells to lyse C215+ **MHC class II**-human colon carcinoma cells, which demonstrates functional substitution of the MHC class II-dependent presentation of SEA with tumor specificity. Treatment of mice carrying B16 melanoma cells expressing a transfected C215 antigen resulted in 95-99% inhibition of tumor growth and allowed long-term survival of animals. The therapeutic effect was dependent on antigen-specific targeting of the FabC215-SEA fusion protein, since native SEA and an antigen-irrelevant FabC242-SEA fusion protein did not influence tumor growth. The results suggest that Fab-SEA fusion proteins convey superantigenicity on tumor cells, which evokes T cells to suppress tumor growth.

AB . . . and the Fab region of the C215 monoclonal antibody specific for human colon carcinoma cells. SEA as part of a **fusion** protein showed a > 10-fold reduction in **MHC class II** binding compared to native SEA, and accordingly, the affinity of the

FabC215-SEA fusion protein for the C215 tumor antigen was approximately 100-fold stronger than to **MHC class II** molecules. The FabC215-SEA **fusion** protein efficiently targeted T cells to lyse C215+ **MHC class II**- human colon carcinoma cells, which demonstrates functional substitution of the MHC class II-dependent presentation of SEA with tumor specificity. Treatment. . .

L2 ANSWER 68 OF 83 MEDLINE DUPLICATE 32
ACCESSION NUMBER: 95016424 MEDLINE
DOCUMENT NUMBER: 95016424 PubMed ID: 7931066
TITLE: Developmental extinction of major histocompatibility complex class II gene expression in plasmocytes is mediated by silencing of the transactivator gene CIITA.
AUTHOR: Silacci P; Mottet A; Steimle V; Reith W; Mach B
CORPORATE SOURCE: L. Jeantet Laboratory of Molecular Genetics, Department of Genetics and Microbiology, University of Geneva Medical School, Switzerland.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Oct 1) 180 (4) 1329-36.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19970203
Entered Medline: 19941102

AB Constitutive major histocompatibility complex (MHC) class II gene expression is tightly restricted to antigen presenting cells and is under developmental control. Cells of the B cell lineage acquire the capacity to express MHC class II genes early during ontogeny and lose this property during terminal differentiation into plasma cells. Cell **fusion** experiments have suggested that the extinction of **MHC class II** expression in plasma cells is due to a dominant repression, but the underlying mechanisms are not understood. CIITA was recently identified as an MHC class II transactivator that is essential for MHC class II expression in B lymphocytes. We show here that inactivation of MHC class II genes in plasmocytes is associated with silencing of the CIITA gene. Moreover, experimentally induced expression of CIITA in plasmocytes leads to reexpression of MHC class II molecules to the same level as that observed on B lymphocytes. We therefore conclude that the loss of MHC class II expression observed upon terminal differentiation of B lymphocytes into plasmocytes results from silencing of the transactivator gene CIITA.

AB . . . to express MHC class II genes early during ontogeny and lose this property during terminal differentiation into plasma cells. Cell **fusion** experiments have suggested that the extinction of **MHC class II** expression in plasma cells is due to a dominant repression, but the underlying mechanisms are not understood. CIITA was recently. . .

L2 ANSWER 69 OF 83 MEDLINE DUPLICATE 33
ACCESSION NUMBER: 95079453 MEDLINE
DOCUMENT NUMBER: 95079453 PubMed ID: 7987867
TITLE: Recruitment of helper T cells for induction of tumour rejection by cytolytic T lymphocytes.
AUTHOR: Stuhler G; Walden P
CORPORATE SOURCE: Max-Planck-Institut fur Biologie, Abteilung Immungenetik, Tubingen, Germany.
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1994 Nov) 39 (5) 342-5.
Journal code: CN3; 8605732. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950124
Last Updated on STN: 19970203
Entered Medline: 19950110

AB Immunotherapy of cancer could be possible in cases in which competent effector T cells can be induced. Such an approach depends on expression of tumour-specific antigens by the tumour cells and on the availability of sufficient costimulatory support for activation of cytotoxic T lymphocytes. Here, a strategy for helper T cell recruitment for induction of tumour-specific cytotoxic immune responses is presented. Allogenic **MHC class II** molecules were introduced into tumour cells by cell **fusion**. These hybrid cells, when injected into mice, induced rejection of an established tumour. The contribution of CD4-expressing helper T cells in the induction phase and of CD8-expressing T cells in the effector phase of the immune response was demonstrated. The approach described could be applicable to cases in which a suitable tumour antigen is present but not identified; it employs regulatory interactions that govern physiological immune responses and is designed to be minimally invasive.

AB . . . T lymphocytes. Here, a strategy for helper T cell recruitment for induction of tumour-specific cytotoxic immune responses is presented. Allogenic **MHC class II** molecules were introduced into tumour cells by cell **fusion**. These hybrid cells, when injected into mice, induced rejection of an established tumour. The contribution of CD4-expressing helper T cells. . .

L2 ANSWER 70 OF 83 MEDLINE DUPLICATE 34
ACCESSION NUMBER: 94275370 MEDLINE
DOCUMENT NUMBER: 94275370 PubMed ID: 8006581
TITLE: Human major histocompatibility complex class II-restricted T cell responses in transgenic mice.
COMMENT: Comment in: J Exp Med. 1994 Jul 1;180(1):11-3
AUTHOR: Woods A; Chen H Y; Trumbauer M E; Sirotina A; Cummings R; Zaller D M
CORPORATE SOURCE: Department of Molecular Immunology, Merck Research Laboratories, Rahway, New Jersey 07065.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Jul 1) 180 (1) 173-81.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940729
Last Updated on STN: 19940729

Entered Medline: 19940721

AB Transgenic mice expressing human major histocompatibility complex (MHC) class II molecules would provide a valuable model system for studying human immunology. However, attempts to obtain human class II-restricted T cell responses in such transgenic mice have had only limited success, possibly due to an inability of mouse CD4 to interact efficiently with human MHC class II molecules. To circumvent this problem, we constructed recombinant MHC class II genes in which the peptide-binding domain was derived from human DR sequences whereas the CD4-binding domain was derived from mouse I-E sequences. Purified **chimeric** human/mouse **MHC class II** molecules were capable of specifically binding DR-restricted peptides. Human B cell transformants that expressed these **chimeric MHC class II** molecules could present peptide antigens to human T cell clones. Expression of these chimeric class II molecules in transgenic mice led to the intrathymic deletion of T cells expressing superantigen-reactive V beta gene segments, indicating that the chimeric class II molecules could influence the selection of the mouse T cell repertoire. These transgenic mice were fully capable of mounting human DR-restricted immune responses after challenge with peptide or whole protein antigens. Thus, the chimeric class II molecules can serve as functional antigen presentation molecules in vivo. In addition, transgenic mice expressing chimeric class II molecules could be used to generate antigen-specific mouse T cell hybridomas that were capable of interacting with human antigen-presenting cells.

AB . . . the peptide-binding domain was derived from human DR sequences whereas the CD4-binding domain was derived from mouse I-E sequences. Purified **chimeric** human/mouse **MHC class II** molecules were capable of specifically binding DR-restricted peptides. Human B cell transformants that expressed these **chimeric MHC class II** molecules could present peptide antigens to human T cell clones. Expression of these chimeric class II molecules in transgenic mice. . .

L2 ANSWER 71 OF 83 MEDLINE DUPLICATE 35
ACCESSION NUMBER: 93219367 MEDLINE
DOCUMENT NUMBER: 93219367 PubMed ID: 8464889
TITLE: Class II-positive hematopoietic cells cannot mediate positive selection of CD4+ T lymphocytes in class II-deficient mice.
AUTHOR: Markowitz J S; Auchincloss H Jr; Grusby M J; Glimcher L H
CORPORATE SOURCE: Department of Cancer Biology, Harvard School of Public Health, Boston, MA 02115.
CONTRACT NUMBER: AI21569 (NIAID)
HL36372 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1993 Apr 1) 90 (7) 2779-83. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199305
ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 19930521
Entered Medline: 19930504

AB Generation of immunocompetent alpha/beta T-cell receptor-positive T cells from CD4+CD8+ thymocytes depends upon their interaction with thymic major histocompatibility complex (MHC) molecules. This process of positive selection provides mature T cells that can recognize antigens in the context of self-MHC proteins. Previous studies investigating haplotype restriction in thymic and bone-marrow chimeras concluded that radioresistant thymic cortical epithelium directs the positive selection of thymocytes. There is controversy, however, as to whether intra- or extrathymic radiosensitive bone marrow-derived macrophage and dendritic cells also can mediate positive selection. To determine whether CD4+ T cells can be positively selected by hematopoietic cells, we generated **chimeric** animals expressing **MHC class II** molecules on either bone marrow-derived or thymic stromal cells by using a recently produced strain of MHC class II-deficient mice. CD4+ T cells developed only when class II MHC molecules were expressed on radioresistant thymic cells. In contrast to what recently has been observed for the selection of CD8+ T lymphocytes, MHC class II-positive bone marrow-derived cells were unable to mediate the selection of CD4+ T cells when the thymic epithelium lacked MHC class II expression. These data suggest that CD4+ and CD8+ T cells may be generated by overlapping, but not identical, mechanisms.

AB . . . also can mediate positive selection. To determine whether CD4+ T cells can be positively selected by hematopoietic cells, we generated **chimeric** animals expressing **MHC class II** molecules on either bone marrow-derived or thymic stromal cells by using a recently produced strain of MHC class II-deficient mice.. . .

L2 ANSWER 72 OF 83 MEDLINE DUPLICATE 36
ACCESSION NUMBER: 93367206 MEDLINE
DOCUMENT NUMBER: 93367206 PubMed ID: 8395547
TITLE: Medullary thymic epithelium expresses a ligand for CTLA4 in situ and in vitro.
AUTHOR: Nelson A J; Hosier S; Brady W; Linsley P S; Farr A G
CORPORATE SOURCE: Department of Biological Structure, University of Washington, Seattle 98195.
CONTRACT NUMBER: AG04360 (NIA)
AI24137 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, (1993 Sep 1) 151 (5) 2453-61. Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19931015
Last Updated on STN: 19931015
Entered Medline: 19930928

AB A fusion protein consisting of the extracellular domain of CTLA4 and an Ig C gamma 1 chain (CTLA4-Ig) was used to examine the distribution of the ligands for CTLA4 within the murine thymus and to characterize the nature of these ligands. Two-color immunofluorescence of thymus tissue revealed binding of the fusion protein to medullary thymic epithelial cells and dendritic cells within the corticomedullary and medullary areas of the thymus. Medullary cells binding the **fusion** protein also expressed **MHC class II** products and ICAM-1. Thymus tissue sections treated with cross-linking fixatives, such as glutaraldehyde, paraformaldehyde, or 1-ethyl-3(3-dimethylaminopropyl)-

carbodiimide no longer bound the CTLA4 fu[redacted] protein, indicating that binding was very sensitive to the tertiary structure of the tissue ligand. The ability of thymic tissue to bind the fusion protein was developmentally regulated. At day 14 of gestation, only scattered single cells were labeled. Clusters of labeled cells, which were detected by day 16 of gestation, increased in frequency with advancing gestational age. Consistent with the in situ labeling studies, CTLA4-Ig also labeled several thymic epithelial cell lines previously shown to have a medullary phenotype. Polymerase chain reaction analysis of mRNA extracted from these cells indicated they contained mRNA for B7, a known counter receptor for CTLA4 and CD28. Immunoprecipitation of 125I-labeled thymic epithelial cells with the CTLA4-Ig detected a M(r) 65,000 to 70,000 species under reducing conditions, consistent with previous studies of B7. These data suggest that the ligand for CTLA4 expressed by thymic epithelial cells in vitro is B7 and that the expression of this ligand in situ is largely restricted to the medullary compartment and is associated with epithelial cells and dendritic cells.

AB . . . medullary thymic epithelial cells and dendritic cells within the corticomedullary and medullary areas of the thymus. Medullary cells binding the **fusion** protein also expressed **MHC class II** products and ICAM-1. Thymus tissue sections treated with cross-linking fixatives, such as glutaraldehyde, paraformaldehyde, or 1-ethyl-3(3-dimethylaminopropyl)-carbodiimide no longer bound the. . .

L2 ANSWER 73 OF 83 MEDLINE DUPLICATE 37
ACCESSION NUMBER: 93289447 MEDLINE
DOCUMENT NUMBER: 93289447 PubMed ID: 8511673
TITLE: New vector for transfer of yeast artificial chromosomes to mammalian cells.
AUTHOR: Markie D; Ragoussis J; Senger G; Rowan A; Sansom D; Trowsdale J; Sheer D; Bodmer W F
CORPORATE SOURCE: Cancer Genetics Laboratory, Imperial Cancer Research Fund, London, U.K.
SOURCE: SOMATIC CELL AND MOLECULAR GENETICS, (1993 Mar) 19 (2) 161-9.
Journal code: UY2; 8403568. ISSN: 0740-7750.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930723
Last Updated on STN: 19930723
Entered Medline: 19930709

AB A modification vector has been constructed to facilitate the transfer of yeast artificial chromosomes (YACs) to mammalian cells in culture by targeting a dominant selectable marker (G418 resistance) to the right arm of pYAC4 clones. The ADE2 gene is used for yeast selection with consequent disruption of the URA3 gene, allowing direct modification of YACs within the common host strain AB1380, and providing a simple test for correct targeting. This vector has been tested by modification of a 550-kb YAC containing part of the human **MHC class II** region and transfer to CHO cells by protoplast **fusion**. Analysis of 15 independent G418-resistant CHO lines obtained following fusion suggests the majority contain a complete YAC with moderate amplification in some lines.

AB . . . test for correct targeting. This vector has been tested by modification of a 550-kb YAC containing part of the human **MHC class II** region and transfer to CHO cells by protoplast **fusion**. Analysis of 15 independent G418-resistant CHO lines obtained following fusion suggests the majority contain a complete YAC with moderate amplification. . .

L2 ANSWER 74 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:505380 CAPLUS
DOCUMENT NUMBER: 117:105380
TITLE: Mitotic recombination of yeast artificial chromosomes
AUTHOR(S): Ragoussis, Jiannis; Trowsdale, John; Markie, David
CORPORATE SOURCE: Hum. Immunogenet., ICRF Lab., London, WC2A 3PX, UK
SOURCE: Nucleic Acids Res. (1992), 20(12), 3135-8
CODEN: NARHAD; ISSN: 0305-1048
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Large regions of human DNA can be cloned and mapped in yeast artificial chromosomes (YACs). Overlapping YAC clones can be used in order to reconstruct genomic segments in vivo by meiotic recombination. This is of importance for reconstruction of a long gene or a gene complex. In this work advantage was taken of yeast protoplast fusion to generate isosexual diploids followed by mitotic crossing-over, and showing that it can be an alternative simple strategy for recombining YACs. Integrative transformation of one of the parent strains with the construct pRAN4 (contg. the ADE2 gene) is used to disrupt the URA3 gene contained within the pYAC4 vector arm, providing the markers required for forcing fusion and detecting recombination. All steps can be carried out within the commonly used AB1380 host strain without the requirement for micromanipulation. The method was applied to YAC clones from the human MHC and resulted in the reconstruction of a 650 kb long single clone contg. 18 known genes from the MHC class II region.

IT Saccharomyces cerevisiae
(YAC mitotic recombination in isosexual diploids from protoplast **fusion** of, human **MHC class II** gene region in relation to)

IT Protoplast and Spheroplast
(isosexual diploids from **fusion** of Saccharomyces cerevisiae, in YAC mitotic recombination, human **MHC class II** gene region in relation to)

IT Mitosis
(recombination during, of YACs, isosexual diploids from protoplast **fusion** for, human **MHC class II** gene region in relation to)

IT Genetic vectors
(YAC, mitotic recombination of, isosexual diploids from protoplast **fusion** for, human **MHC class II** gene region in relation to)

IT Recombination, genetic
(mitotic, of YACs, isosexual diploids from protoplast **fusion** for, human **MHC class II** gene region in relation to)

L2 ANSWER 75 OF 83 MEDLINE DUPLICATE 38
ACCESSION NUMBER: 93018877 MEDLINE
DOCUMENT NUMBER: 93018877 PubMed ID: 1402690

TITLE: Reactivation of a major histocompatibility complex class II gene in mouse plasmacytoma cells and mouse T cells.
AUTHOR: Chang C H; Fodor W L; Flavell R A
CORPORATE SOURCE: Howard Hughes Medical Institute, Section of Immunobiology, Yale University School of Medicine, Connecticut 06510.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1992 Nov 1) 176 (5) 1465-9.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921125

AB Terminally differentiated plasma cells and mouse T cells do not express major histocompatibility complex (MHC) class II genes although class II gene expression is observed in pre-B and mature B cells as well as in activated human T cells. Transient heterokaryons were prepared and analyzed to investigate the mechanisms of inactivation of MHC class II gene in mouse plasmacytoma cells and mouse T cells. The endogenous MHC class II genes in both mouse plasmacytoma cells and mouse T cells can be reactivated by factors present in B cells. This reactivation of class II gene is also observed by **fusion** with a human T cell line which expresses **MHC class II** genes, but not with a class II negative human T cell line. It appears that the loss of MHC class II gene expression during the terminal differentiation of B cells or T cell lineage is due to absence of positive regulatory factor(s) necessary for class II transcription.

AB . . . cells can be reactivated by factors present in B cells. This reactivation of class II gene is also observed by **fusion** with a human T cell line which expresses **MHC class II** genes, but not with a class II negative human T cell line. It appears that the loss of MHC class. . .

L2 ANSWER 76 OF 83 MEDLINE DUPLICATE 39
ACCESSION NUMBER: 92091784 MEDLINE
DOCUMENT NUMBER: 92091784 PubMed ID: 1727871
TITLE: Expression of a functional **chimeric** Ig-**MHC class II** protein.
AUTHOR: Zwirner J; Weissenhorn W; Karlsson L; Becker A; Rieber E P; Riethmuller G; Weiss E H; Peterson P A; Widera G
CORPORATE SOURCE: Department of Immunology, Scripps Research Institute, La Jolla, CA 92037.
SOURCE: JOURNAL OF IMMUNOLOGY, (1992 Jan 1) 148 (1) 272-6.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199201
ENTRY DATE: Entered STN: 19920216
Last Updated on STN: 19920216
Entered Medline: 19920127

AB We have generated a chimeric protein molecule composed of the alpha- and beta-chains of the MHC class II I-E molecule fused to antibody V regions derived from anti-human CD4 mAb MT310. Expression vectors were constructed containing the functional, rearranged gene segments coding for the V region domains of the antibody H and L chains in place of the first domains of the complete structural genes of the I-E alpha- and beta-chains, respectively. Cells transfected with both hybrid genes expressed a stable protein product on the cell surface. The chimeric molecule exhibited the idiotype of the antibody MT310 as shown by binding to the anti-idiotypic mAb 20-46. A protein of the anticipated molecular mass was immunoprecipitated with anti-mouse IgG antiserum. Furthermore, human soluble CD4 did bind to the transfected cell line, demonstrating that the chimeric protein possessed the binding capacity of the original mAb. Thus, the hybrid molecule retained: 1) the properties of a MHC class II protein with regard to correct chain assembly and transport to the cell surface; as well as 2) the Ag binding capacity of the antibody genes used. The generation of hybrid MHC class II molecules with highly specific, non-MHC-restricted binding capacities will be useful for studying MHC class II-mediated effector functions such as selection of the T cell repertoire in thymus of transgenic mice.

TI Expression of a functional **chimeric** Ig-**MHC class II** protein.

L2 ANSWER 77 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:569106 CAPLUS
DOCUMENT NUMBER: 117:169106
TITLE: Immunogenic targeting of subunit HIV-1 peptide vaccines to antigen-presenting cells by chimeric anti-MHC antibodies
AUTHOR(S): Baier, Gottfried; Giampa, Leslie; Altman, Amnon
CORPORATE SOURCE: La Jolla Inst. Allergy Immunol., La Jolla, CA, 92037, USA
SOURCE: Vaccines 92: Mod. Approaches New Vaccines Incl. Prev. AIDS [Annu. Meet.], 9th (1992), 205-10. Editor(s): Brown, Fred. Cold Spring Harbor Lab. Press: Cold Spring Harbor, N. Y.
CODEN: 57WXAL
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Synthetic peptides encompassing pathogen-derived T-cell plus B-cell epitopes can function as complete immunogens that elicit neutralizing antibodies and T-cell memory. Their use is limited, however, because of the MHC-restricted nature of T-cell responses and their inherently weak immunogenicity. To address these problems, recombinant DNA techniques were used to generate **chimeric** anti-**MHC class II** antibody Fab fragments that express HIV-1-derived immunogenic T-cell plus B-cell epitopes contained within the immunodominant V3 loop region of the envelope glycoprotein, gp120. Such chimeric Fab fragments were cloned, expressed, and characterized by mol. and immunochem. means. Their expression in Escherichia coli was optimized to a level of .apprx.500 .mu.g/L of culture using a T7 promoter-based expression system. Such bacterially derived chimeric anti-MHC Fab fragments are expected to target the HIV-1 epitopes to, and focus them at high d. on, the surface of antigen presenting cells leading to a more efficient antigen presentation. This approach is likely to potentiate the immune response (neutralizing antibodies, cell-mediated immunity, and immunol. memory) against HIV-1, thereby possibly reducing the no. of booster injections and providing built-in adjuvant activity.

AB Synthetic peptides encompassing pathogen-derived T-cell plus B-cell epitopes can function as complete immunogens that elicit neutralizing antibodies and T-cell memory. Their use is limited, however, because of the MHC-restricted nature of T-cell responses and their inherently weak immunogenicity. To address these problems, recombinant DNA techniques were used to generate **chimeric** anti-**MHC class II** antibody Fab fragments that express HIV-1-derived immunogenic T-cell plus B-cell epitopes contained within the immunodominant V3 loop region of the envelope glycoprotein, gp120. Such chimeric Fab fragments were cloned, expressed, and characterized by mol. and immunochem. means. Their expression in Escherichia coli was optimized to a level of .apprx.500 .mu.g/L of culture using a T7 promoter-based expression system. Such bacterially derived chimeric anti-MHC Fab fragments are expected to target the HIV-1 epitopes to, and focus them at high d. on, the surface of antigen presenting cells leading to a more efficient antigen presentation. This approach is likely to potentiate the immune response (neutralizing antibodies, cell-mediated immunity, and immunol. memory) against HIV-1, thereby possibly reducing the no. of booster injections and providing built-in adjuvant activity.

L2 ANSWER 78 OF 83 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:318446 BIOSIS
DOCUMENT NUMBER: BR43:19171
TITLE: ANTIGEN PRESENTATION BY **CHIMERIC** MOUSE HUMAN **MHC CLASS II** MOLECULES.
AUTHOR(S): ZALLER D M; WOODS A
CORPORATE SOURCE: DEP. MOL. IMMUNOL., MERCK SHARP DOHME RES. LAB., RAHWAY, N.J. 07065, USA.
SOURCE: KEYSTONE SYMPOSIUM ON ANTIGEN PRESENTATION FUNCTIONS OF THE MHC (MAJOR HISTOCOMPATIBILITY COMPLEX), TAOS, NEW MEXICO, USA, MARCH 5-11, 1992. J CELL BIOCHEM SUPPL, (1992) 0 (16 PART D), 84.
CODEN: JCBSD7.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English
TI ANTIGEN PRESENTATION BY **CHIMERIC** MOUSE HUMAN **MHC CLASS II** MOLECULES.

L2 ANSWER 79 OF 83 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:318778 BIOSIS
DOCUMENT NUMBER: BR43:19503
TITLE: IMMUNOGENIC TARGETING OF SYNTHETIC HIV-1 PEPTIDE VACCINES TO APCS BY **CHIMERIC** ANTI-**MHC CLASS II** AND ANTI-SIGD ANTIBODIES.
AUTHOR(S): BAIER G; GIAMPA L; ALTMAN A
CORPORATE SOURCE: LA JOLLA INSTITUTE ALLERGY IMMUNOLOGY, 11149 NORTH TORREY PINES ROAD, LA JOLLA, CALIF. 92037.
SOURCE: KEYSTONE SYMPOSIUM ON PREVENTION AND TREATMENT OF AIDS, KEYSTONE, COLORADO, USA, MARCH 27-APRIL 3, 1992. J CELL BIOCHEM SUPPL, (1992) 0 (16 PART E), 59.
CODEN: JCBSD7.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English
TI IMMUNOGENIC TARGETING OF SYNTHETIC HIV-1 PEPTIDE VACCINES TO APCS BY **CHIMERIC** ANTI-**MHC CLASS II** AND ANTI-SIGD ANTIBODIES.

L2 ANSWER 80 OF 83 MEDLINE DUPLICATE 40
ACCESSION NUMBER: 91147127 MEDLINE
DOCUMENT NUMBER: 91147127 PubMed ID: 1847691
TITLE: MHC class II-restricted T-cell hybridomas recognizing the nucleocapsid protein of avian coronavirus IBV.
AUTHOR: Boots A M; Van Lierop M J; Kusters J G; Van Kooten P J; Van der Zeijst B A; Hensen E J
CORPORATE SOURCE: Institute of Molecular Biology and Medical Biotechnology, University of Utrecht, The Netherlands.
SOURCE: IMMUNOLOGY, (1991 Jan) 72 (1) 10-4.
Journal code: GH7; 0374672. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199104
ENTRY DATE: Entered STN: 19910419
Last Updated on STN: 19980206
Entered Medline: 19910404
AB Mice were immunized with purified infectious bronchitis virus (IBV), strain M41. Spleen cells, expanded in vitro by stimulation with M41, were immortalized by **fusion** to obtain T-cell hybridomas, and two major histocompatability complex (**MHC**) **class II** (I-E)-restricted T-cell hybridomas were selected with specificity for IBV. Both hybridomas selectively recognized the internal nucleocapsid protein. The responses to 12 different strains of IBV varied markedly. This demonstrates antigenic variation of the nucleocapsid protein in addition to the known variation of the surface glycoprotein S.
AB . . . with purified infectious bronchitis virus (IBV), strain M41. Spleen cells, expanded in vitro by stimulation with M41, were immortalized by **fusion** to obtain T-cell hybridomas, and two major histocompatability complex (**MHC**) **class II** (I-E)-restricted T-cell hybridomas were selected with specificity for IBV. Both hybridomas selectively recognized the internal nucleocapsid protein. The responses to. . .

L2 ANSWER 81 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:508786 CAPLUS
DOCUMENT NUMBER: 113:108786
TITLE: Recombinant CD4-Pseudomonas exotoxin hybrid protein displays HIV-specific cytotoxicity without affecting MHC Class II-dependent functions
AUTHOR(S): Berger, Edward A.; Chaudhary, Vijay K.; Clouse, Kathleen A.; Jaraquemada, Dolores; Nicholas, Judith A.; Rubino, Kathleen L.; Fitzgerald, David J.; Pastan, Ira; Moss, Bernard
CORPORATE SOURCE: Natl. Inst. Allergy Infect. Dis., NIH, Bestheda, MD, 20892, USA
SOURCE: AIDS Res. Hum. Retroviruses (1990), 6(6), 795-804
CODEN: ARHRE7; ISSN: 0889-2229
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study describes several in vitro activities of CD4(178)-PE40, a recombinant protein contg. a portion of human CD4 linked to active

regions of Pseudomonas aeruginosa exotoxin A. In assays for cell viability, the hybrid toxin displays highly selective cytotoxicity for HIV-infected T lymphocytes. In a latently infected human T-cell line which is inducible for HIV expression, toxin sensitivity is obsd. only upon virus induction. At concns. which readily kill HIV-infected T cells, CD4(178)-PE40 has no observable cytotoxic effects on uninfected human cell lines expressing surface major histocompatibility complex (MHC) Class II mols., and does not interfere with cellular responses known to be dependent on functional assocn. between CD4 and MHC Class II mols.

IT Toxins
RL: BIOL (Biological study)
(exo-, A, **fusion** product with antigen CD4, HIV-specific cytotoxicity of, **MHC Class II**-dependent functions in relation to)

L2 ANSWER 82 OF 83 MEDLINE DUPLICATE 41
ACCESSION NUMBER: 88261279 MEDLINE
DOCUMENT NUMBER: 88261279 PubMed ID: 3133552
TITLE: Two distinct nuclear factors bind the conserved regulatory sequences of a rabbit major histocompatibility complex class II gene.
AUTHOR: Sittisombut N
CORPORATE SOURCE: Department of Microbiology and Immunology, College of Medicine, University of Illinois, Chicago 60612.
CONTRACT NUMBER: AI 11234-15 (NIAID)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1988 May) 8 (5) 2034-41. Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198807
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880729

AB The constitutive coexpression of the major histocompatibility complex (MHC) class II genes in B lymphocytes requires positive, trans-acting transcriptional factors. The need for these trans-acting factors has been suggested by the reversion of the **MHC class II**-negative phenotype of rare B-lymphocyte mutants through somatic cell **fusion** with B cells or T-cell lines. The mechanism by which the trans-acting factors exert their effect on gene transcription is unknown. The possibility that two highly conserved DNA sequences, located 90 to 100 base pairs (bp) (the A sequence) and 60 to 70 bp (the B sequence) upstream of the transcription start site of the class II genes, are recognized by the trans-acting factors was investigated in this study. By using the gel electrophoresis retardation assay, a minimum of two proteins which specifically bound the conserved A or B sequence of a rabbit DP beta gene were identified in murine nuclear extracts of a B-lymphoma cell line, A20-2J. Fractionation of nuclear extract through a heparin-agarose column allowed the identification of one protein, designated NF-MHCIIB, which bound an oligonucleotide containing the B sequence and protected the entire B sequence in the DNase I protection analysis. Another protein, designated NF-MHCIIA, which bound an oligonucleotide containing the A sequence and partially protected the 3' half of this sequence, was also identified. NF-MHCIIB did not protect a CCAAT sequence located 17 bp downstream of the B sequence. The possible relationship between these DNA-binding factors and the trans-acting factors identified in the cell fusion experiments is discussed.

AB . . . lymphocytes requires positive, trans-acting transcriptional factors. The need for these trans-acting factors has been suggested by the reversion of the **MHC class II**-negative phenotype of rare B-lymphocyte mutants through somatic cell **fusion** with B cells or T-cell lines. The mechanism by which the trans-acting factors exert their effect on gene transcription is. . .

L2 ANSWER 83 OF 83 MEDLINE DUPLICATE 42
ACCESSION NUMBER: 88055289 MEDLINE
DOCUMENT NUMBER: 88055289 PubMed ID: 3500056
TITLE: A phenotypically dominant regulatory mechanism suppresses major histocompatibility complex class II gene expression in a murine plasmacytoma.
AUTHOR: Venkitaraman A R; Culbert E J; Feldmann M
CORPORATE SOURCE: Immunology Unit, Charing Cross Sunley Research Centre, London, GB.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1987 Oct) 17 (10) 1441-6. Journal code: EN5; 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198712
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19970203
Entered Medline: 19871221

AB The expression of major histocompatibility complex (MHC) class II antigens is down-regulated when B cells differentiate into plasma cells. We have studied the mechanism of down-regulation of MHC class II expression in a BALB/c strain-derived murine plasmacytoma cell line, NS1. NS1 cells express MHC class I antigens but not MHC class II antigens. We tested 20 uncloned hybrid cell lines obtained from the **fusion** of NS1 cells with **MHC class II**-expressing splenic B cells prepared from CBA, SJL or BALB/c mice. All the hybrid cell lines expressed MHC class I antigens of either or both parental haplotypes but did not express MHC class II. One NS1 X splenic B cell hybrid clone, K3, was used to further validate these results; K3 cells expressed MHC class I but not MHC class II antigens. K3 was fused to the MHC class II-expressing B lymphoma A20, and the seven resulting hybrid cell lines were again found to express MHC class I but not MHC class II antigens. Since NS1 is a subclone of the P3-X63Ag8 murine plasmacytoma, we also tested one P3-X63Ag8 x splenic B cell hybrid, Sp2/0, and two Sp2/0 x splenic B cell hybrids. All were found to express the appropriate MHC class I antigens but did not express MHC class II. Thus, our results suggest that the NS1 plasmacytoma suppresses MHC class II expression by a phenotypically dominant regulatory mechanism. We found that NS1 cells express correctly sized mRNA for the MHC class II genes A alpha, E alpha and the invariant chain. The co-expression of MHC class I protein and I-A and I-E region gene transcripts provides strong evidence that the MHC gene cluster is structurally intact, and that lack of class II expression is due to a genetic regulatory mechanism. The amounts of class II mRNA expressed by NS1 cells were at least equivalent to those found in splenic lymphocytes. Therefore, this regulation must operate post-transcriptionally.

AB . . . MHC class I antigens but not MHC class II antigens. We tested 20

uncloned hybrid cell lines obtained from the fusion of NS1 cells
with MHC class II-expressing splenic B cells
prepared from CBA, SJL or BALB/c mice. All the hybrid cell lines expressed
MHC class I antigens. . .

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 NEWS  2  Dec 17  The CA Lexicon available in the CAPLUS and CA files
 NEWS  3  Feb 06  Engineering Information Encompass files have new names
 NEWS  4  Feb 16  TOXLINE no longer being updated
 NEWS  5  Apr 23  Search Derwent WPINDEX by chemical structure
 NEWS  6  Apr 23  PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS  7  May 07  DGENE Reload
 NEWS  8  Jun 20  Published patent applications (A1) are now in USPATFULL
 NEWS  9  JUL 13  New SDI alert frequency now available in Derwent's
                  DWPI and DPCI

 NEWS EXPRESS  July 11 CURRENT WINDOWS VERSION IS V6.0b,
               CURRENT MACINTOSH VERSION IS V5.0C (ENG) AND V5.0JB (JP),
               AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2001
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=> s tetramer (10N) (MHC or Class I or Class II)
L1          535 TETRAMER (10N) (MHC OR CLASS I OR CLASS II)

=> s tetramer (10N) (MHC or HLA or Class II or DR?)
   3 FILES SEARCHED...
L2          967 TETRAMER (10N) (MHC OR HLA OR CLASS II OR DR?)

=> s tetramer (10N) (MHC or HLA? or Class II)
L3          682 TETRAMER (10N) (MHC OR HLA? OR CLASS II)

=> s l3 and PD<1999
'1999' NOT A VALID FIELD CODE
   2 FILES SEARCHED...
   3 FILES SEARCHED...
L4           51 L3 AND PD<1999

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           27 DUP REM L4 (24 DUPLICATES REMOVED)

=> dis 15 1-27 ibib abs kwic

L5   ANSWER 1 OF 27  CAPLUS  COPYRIGHT 2001 ACS        DUPLICATE 1
ACCESSION NUMBER:         1998:612255  CAPLUS
DOCUMENT NUMBER:          129:314733
TITLE:                    Importance of a conserved TCR J .alpha.-encoded
                          tyrosine for T cell recognition of an HLA B27/peptide
                          complex
AUTHOR(S):                Bowness, Paul; Allen, Rachel L.; Barclay, Douglas N.;
                          Jones, E. Yvonne; McMichael, Andrew J.
CORPORATE SOURCE:         Molecular Immunology Group, Institute Molecular
                          Medicine, John Radcliffe Hospital, University Oxford,
                          Oxford, OX3 9DS, UK
SOURCE:                   Eur. J. Immunol. (1998), 28(9), 2704-2713
                          CODEN: EJIMAF; ISSN: 0014-2980
PUBLISHER:                Wiley-VCH Verlag GmbH
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Human HLA B27-restricted cytotoxic T lymphocytes (CTL) specific for the
     influenza A epitope NP383-391 use similar TCR .alpha. and .beta. chains,
     with 2 closely related J.alpha. segments used by 6 of nine CTL clones from
     3 unrelated donors.  The role of TCR complementarity-detg. region
     (CDR)3.alpha. residues 93 and 100-102 were examd. by site-directed
     mutagenesis, following expression of the TCR .alpha. and .beta.
     extracellular domains from 1 clone as a TCR .zeta. fusion heterodimer in
     rat basophil leukemia (RBL) cells.  For the 1st time the authors have
```

measured direct binding of tetrameric HL[redacted]705/NP383-391 complexes to transfected TCR. Independently peptide-pulsed antigen-presenting cells (APC) were used to induce TCR-mediated degranulation of RBL transfectants. The results show a key role for the conserved TCR.alpha. CDR3 J.alpha.-encoded residue Y102 in recognition of HLA B27/NP383-391. Thus the Y102D mutation abolished both tetramer binding and degranulation in the presence of peptide-pulsed APC. Even the Y102F mutation, differing only by a single hydroxyl group from the native TCR, abolished detectable degranulation. Further mutations F93A and S100R also abolished recognition. The N101A mutation recognized **HLA** 827/NP in functional assays despite having reduced **tetramer** binding, a finding consistent with "kinetic editing" models of T cell activation. Modeling of the GRb TCR CDR3.alpha. loop suggests that residue Y102 contacts the HLA 8*2705 .alpha.1 helix. It is thus possible that selection of germ-line TCRAJ-encoded residues at position 102 may be MHC driven.

SO Eur. J. Immunol. (**1998**), 28(9), 2704-2713
CODEN: EJIMAF; ISSN: 0014-2980

AB Human HLA B27-restricted cytotoxic T lymphocytes (CTL) specific for the influenza A epitope NP383-391 use similar TCR .alpha. and .beta. chains, with 2 closely related J.alpha. segments used by 6 of nine CTL clones from 3 unrelated donors. The role of TCR complementarity-detg. region (CDR)3.alpha. residues 93 and 100-102 were examd. by site-directed mutagenesis, following expression of the TCR .alpha. and .beta. extracellular domains from 1 clone as a TCR .zeta. fusion heterodimer in rat basophil leukemia (RBL) cells. For the 1st time the authors have measured direct binding of tetrameric HLA B*2705/NP383-391 complexes to transfected TCR. Independently peptide-pulsed antigen-presenting cells (APC) were used to induce TCR-mediated degranulation of RBL transfectants. The results show a key role for the conserved TCR.alpha. CDR3 J.alpha.-encoded residue Y102 in recognition of HLA B27/NP383-391. Thus the Y102D mutation abolished both tetramer binding and degranulation in the presence of peptide-pulsed APC. Even the Y102F mutation, differing only by a single hydroxyl group from the native TCR, abolished detectable degranulation. Further mutations F93A and S100R also abolished recognition. The N101A mutation recognized **HLA** 827/NP in functional assays despite having reduced **tetramer** binding, a finding consistent with "kinetic editing" models of T cell activation. Modeling of the GRb TCR CDR3.alpha. loop suggests that residue Y102 contacts the HLA 8*2705 .alpha.1 helix. It is thus possible that selection of germ-line TCRAJ-encoded residues at position 102 may be MHC driven.

L5 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:398958 CAPLUS
DOCUMENT NUMBER: 129:160353
TITLE: Phenotypic analysis of antigen-specific T lymphocytes. [Erratum to document cited in CA125:245038]
AUTHOR(S): Altman, John D.; Moss, Paul A. H.; Goulder, Philip J. R.; Barouch, Dan H.; McHeyzer-Williams, Michael G.; Bell, John I.; McMichael, Andrew J.; Davis, Mark M.
CORPORATE SOURCE: Sch. Medicine, Stanford Univ., Stanford, CA, 94305-5428, USA
SOURCE: Science (Washington, D. C.) (**1998**), 280(5371), 1821
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An error occurred in the 3' oligonucleotide used to create the HLA-A*0201 plasmid contg. the biotinylated substrate peptide tag.

SO Science (Washington, D. C.) (**1998**), 280(5371), 1821
CODEN: SCIEAS; ISSN: 0036-8075

IT **HLA**-A2 antigen
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(biotinylated, sol. **tetramers**, complexes with peptides; for phenotypic anal. of antigen-specific T-cells (Erratum))

L5 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:717543 CAPLUS
DOCUMENT NUMBER: 130:80046
TITLE: Ex vivo staining of metastatic lymph nodes by class I major histocompatibility complex tetramers reveals high numbers of antigen-experienced tumor-specific cytolytic T lymphocytes
AUTHOR(S): Romero, Pedro; Dunbar, P. Rod; Valmori, Danila; Pittet, Mikael; Ogg, Graham S.; Rimoldi, Donata; Chen, Ji-Li; Lienard, Danielle; Cerottini, Jean-Charles; Cerundolo, Vincenzo
CORPORATE SOURCE: Division of Clinical Onco-Immunology, Ludwig Institute for Cancer Research, Lausanne Branch, Centre Hospitalier Universitaire Vaudois, Lausanne, 1011, Switz.
SOURCE: J. Exp. Med. (**1998**), 188(9), 1641-1650
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Characterization of cytolytic T lymphocyte (CTL) responses to tumor antigens has been impeded by a lack of direct assays of CTL activity. The authors have synthesized reagents ("tetramers") that specifically stain CTLs recognizing melanoma antigens. Tetramer staining of tumor-infiltrated lymph nodes ex vivo revealed high frequencies of tumor-specific CTLs which were antigen-experienced by surface phenotype. In vitro culture of lymph node cells with cytokines resulted in very large expansions of tumor-specific CTLs that were dependent on the presence of tumor cells in the lymph nodes. Tetramer-guided sorting by flow cytometer allowed isolation of melanoma-specific CTLs and confirmation of their specificity and their ability to lyse autologous tumor cells. These results demonstrate the value of these novel reagents for monitoring tumor-specific CTL responses and for generating CTLs for adoptive immunotherapy. These data also indicate that strong CTL responses to melanoma often occur in vivo, and that the reactive CTLs have substantial proliferative and tumoricidal potential.

REFERENCE COUNT: 22
REFERENCE(S): (1) Altman, J; Science 1996, V274, P94 CAPLUS
(3) de Vries, T; Cancer Res 1997, V57, P3223 CAPLUS
(4) Dunbar, P; Curr Biol 1998, V8, P413 CAPLUS
(5) Ferrone, S; Immunol Today 1995, V16, P487 CAPLUS
(6) Hahne, M; Science 1996, V274, P1363 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO J. Exp. Med. (**1998**), 188(9), 1641-1650

CODEN: JEMEAV; ISSN: 0022-1007

IT Melanoma-associated antigen
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Melan-A/MART-1; enumeration of melanoma-reactive cytotoxic T-cells in tumor-infiltrated lymph nodes using sol. MHC class I complex **tetramers** contg. peptide of)

IT HLA-A2 antigen
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(complexes, with melanoma antigens; enumeration of melanoma-reactive cytotoxic T-cells in tumor-infiltrated lymph nodes using sol. MHC class I/peptide complex **tetramers**)

IT Adoptive immunotherapy
Cytotoxic T cell
Fluorescent staining (biological)
Lymph node tumors
Melanoma metastasis
T cell infiltration
(enumeration of melanoma-reactive cytotoxic T-cells in tumor-infiltrated lymph nodes using sol. MHC class I/peptide complex **tetramers**)

IT 9002-10-2, Tyrosinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(enumeration of melanoma-reactive cytotoxic T-cells in tumor-infiltrated lymph nodes using sol. MHC class I complex **tetramers** contg. peptide of)

IT 168650-46-2D, sol. HLA-A2 complexes 204060-45-7D, sol. HLA-A2 complexes
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(enumeration of melanoma-reactive cytotoxic T-cells in tumor-infiltrated lymph nodes using sol. MHC class I/peptide complex **tetramers**)

L5 ANSWER 4 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:285064 CAPLUS
DOCUMENT NUMBER: 129:66582
TITLE: Induction and exhaustion of lymphocytic choriomeningitis virus-specific cytotoxic T lymphocytes visualized using soluble tetrameric major histocompatibility complex class I-peptide complexes
AUTHOR(S): Gallimore, Awen; Glithero, Ann; Godkin, Andrew; Tissot, Alain C.; Pluckthun, Andreas; Elliott, Tim; Hengartner, Hans; Zinkernagel, Rolf
CORPORATE SOURCE: Institute of Experimental Immunology, Zurich, CH-8091, Switz.
SOURCE: J. Exp. Med. (**1998**), 187(9), 1383-1393
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study describes the construction of sol. major histocompatibility complexes consisting of the mouse class I mol., H-2Db, chem. biotinylated .beta.2 microglobulin and a peptide epitope derived from the glycoprotein (GP; amino acids 33-41) of lymphocytic choriomeningitis virus (LCMV). Tetrameric class I complexes, which were produced by mixing the class I complexes with phycoerythrin-labeled neutravidin, permitted direct anal. of virus-specific cytotoxic T lymphocytes (CTLs) by flow cytometry. This technique was validated by (a) staining CD8+ cells in the spleens of transgenic mice that express a T cell receptor (TCR) specific for H-2Db in assocn. with peptide GP33-41, and (b) by staining virus-specific CTLs in the cerebrospinal fluid of C57BL/6 (B6) mice that had been infected intracranially with LCMV-DOCILE. Staining of spleen cells isolated from B6 mice revealed that up to 40% of CD8+ T cells were GP33 tetramer+ during the initial phase of LCMV infection. In contrast, GP33 tetramers did not stain CD8+ T cells isolated from the spleens of B6 mice that had been infected 2 mo previously with LCMV above the background levels found in naive mice. The fate of virus-specific CTLs was analyzed during the acute phase of infection in mice challenged both intracranially and i.v. with a high or low dose of LCMV-DOCILE. The results of the study show that the outcome of infection by LCMV is detd. by antigen load alone. Furthermore, the data indicate that deletion of virus-specific CTLs in the presence of excessive antigen is preceded by TCR downregulation and is dependent upon perforin.

SO J. Exp. Med. (**1998**), 187(9), 1383-1393
CODEN: JEMEAV; ISSN: 0022-1007

IT Phycoerythrins
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(conjugates, with neutravidin; lymphocytic choriomeningitis virus-specific cytotoxic T-cells visualized using sol. MHC class I-peptide **tetramers** with)

IT 58-85-5D, Biotin, .beta.2-microglobulin conjugates 157885-16-0D, Neutravidin, phycoerythrin conjugates
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(lymphocytic choriomeningitis virus-specific cytotoxic T-cells visualized using sol. MHC class I-peptide **tetramers** with)

L5 ANSWER 5 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
ACCESSION NUMBER: 1998:646169 CAPLUS
DOCUMENT NUMBER: 129:342623
TITLE: High frequency of skin-homing melanocyte-specific cytotoxic T lymphocytes in autoimmune vitiligo
AUTHOR(S): Ogg, Graham S.; Dunbar, P. Rod; Romero, Pedro; Chen, Ji-Li; Cerundolo, Vincenzo
CORPORATE SOURCE: Nuffield Department of Clinical Medicine, Institute of Molecular Medicine, Oxford, OX3 9DS, UK
SOURCE: J. Exp. Med. (**1998**), 188(6), 1203-1208
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Vitiligo is an autoimmune condition characterized by loss of epidermal melanocytes. Using tetrameric complexes of human histocompatibility leukocyte antigen (HLA) class I to identify antigen-specific T cells ex vivo, the authors obsd. high frequencies of circulating MelanA-specific, A*0201-restricted cytotoxic T lymphocytes (A2-MelanA **tetramer**+ CTLs) in seven of nine HLA-A*0201-pos. individuals with vitiligo. Isolated A2-MelanA tetramer+ CTLs were able to lyse A*0201-matched melanoma cells in vitro and their frequency ex vivo correlated with extent of disease. In contrast, no A2-MelanA tetramer+ CTL could be identified ex vivo in all four A*0201-neg. vitiligo patients or five of six A*0201-pos. asymptomatic controls. Finally, the authors obsd. that the A2-MelanA tetramer+ CTLs isolated from vitiligo patients expressed high levels of the skin homing receptor, cutaneous

lymphocyte-assocd. antigen, which was absent from the CTLs seen in the single A*0201-pos. normal control. These data are consistent with a role of skin-homing autoreactive melanocyte-specific CTLs in causing the destruction of melanocytes seen in autoimmune vitiligo. Lack of homing receptors on the surface of autoreactive CTLs could be a mechanism to control peripheral tolerance in vivo.

SO J. Exp. Med. (1998), 188(6), 1203-1208
CODEN: JEMEAV; ISSN: 0022-1007

AB Vitiligo is an autoimmune condition characterized by loss of epidermal melanocytes. Using tetrameric complexes of human histocompatibility leukocyte antigen (HLA) class I to identify antigen-specific T cells ex vivo, the authors obsd. high frequencies of circulating MelanA-specific, A*0201-restricted cytotoxic T lymphocytes (A2-MelanA **tetramer**+ CTLs) in seven of nine **HLA**-A*0201-pos. individuals with vitiligo. Isolated A2-MelanA tetramer+ CTLs were able to lyse A*0201-matched melanoma cells in vitro and their frequency ex vivo correlated with extent of disease. In contrast, no A2-MelanA tetramer+ CTL could be identified ex vivo in all four A*0201-neg. vitiligo patients or five of six A*0201-pos. asymptomatic controls. Finally, the authors obsd. that the A2-MelanA tetramer+ CTLs isolated from vitiligo patients expressed high levels of the skin homing receptor, cutaneous lymphocyte-assocd. antigen, which was absent from the CTLs seen in the single A*0201-pos. normal control. These data are consistent with a role of skin-homing autoreactive melanocyte-specific CTLs in causing the destruction of melanocytes seen in autoimmune vitiligo. Lack of homing receptors on the surface of autoreactive CTLs could be a mechanism to control peripheral tolerance in vivo.

L5 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:689142 CAPLUS
DOCUMENT NUMBER: 130:93975
TITLE: Direct visualization of antigen-specific cytotoxic T cells -- a new insight into immune defenses
AUTHOR(S): Schwartz, Robert S.
CORPORATE SOURCE: USA
SOURCE: N. Engl. J. Med. (1998), 339(15), 1076-1078
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 3 refs. discussing the application of **HLA** class I/peptide **tetramers** for the immunofluorescent measurement of cytotoxic T-cells.

REFERENCE COUNT: 3
REFERENCE(S): (1) Altman, J; Science 1996, V274, P94 CAPLUS
(2) Callan, M; J Exp Med 1998, V187, P1395 CAPLUS
(3) Ogg, G; Science 1998, V279, P2103 CAPLUS

SO N. Engl. J. Med. (1998), 339(15), 1076-1078
CODEN: NEJMAG; ISSN: 0028-4793

AB A review with 3 refs. discussing the application of **HLA** class I/peptide **tetramers** for the immunofluorescent measurement of cytotoxic T-cells.

IT Flow cytometry
(FACS (fluorescence-activated cell sorting); **HLA** class I/peptide **tetramers** for visualization of antigen-specific cytotoxic T-cells by)

IT Cytotoxic T cell
(**HLA** class I/peptide **tetramers** for visualization of)

L5 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
ACCESSION NUMBER: 1998:134074 CAPLUS
DOCUMENT NUMBER: 128:269312
TITLE: HLA-E binds to natural killer cell receptors CD94/NKG2A, B and C
AUTHOR(S): Braud, Veronique M.; Allan, David S. J.; O'Callaghan, Christopher A.; Soderstrom, Kalle; D'Andrea, Annalisa; Ogg, Graham S.; Lazatic, Sasha; Young, Neil T.; Bell, John I.; Phillips, Joseph H.; Lanier, Lewis L.; McMichael, Andrew J.
CORPORATE SOURCE: Inst. Molecular Med., John Radcliffe Hosp., Oxford, OX3 9DS, UK
SOURCE: Nature (London) (1998), 391(6669), 795-799
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The protein HLA-E is a non-classical major histocompatibility complex (MHC) mol. of limited sequence variability. Its expression on the cell surface is regulated by the binding of peptides derived from the signal sequence of some other MHC class I mols. Here we report the identification of ligands for HLA-E. We constructed **tetramers** in which recombinant **HLA**-E and .beta.2-microglobulin were refolded with an MHC, leader-sequence peptide, biotinylated, and conjugated to phycoerythrin-labeled Extravidin. This **HLA**-E **tetramer** bound to natural killer (NK) cells and a small subset of T cells from peripheral blood. On transfectants, the tetramer bound to the CD94/NKG2A, CD94/NKGK2B and CD94/NKG2C NM cell receptors, but did not bind to the Ig family of NK cell receptors (KIR). Surface expression of HLA-E was enough to protect target cells from lysis by CD94/NKG2A+ NK-cell clones. A subset of HLA class I alleles has been shown to inhibit killing by CD94/NKG2A+ NK-cell clones. Only the HLA alleles that posses a leader peptide capable of upregulating HLA-E surface expression confer resistance to NK-cell-mediated lysis, implying that their action is mediated by HLA-E, the predominant ligand for the NK cell inhibitory receptor CD94/NKG2A.

SO Nature (London) (1998), 391(6669), 795-799
CODEN: NATUAS; ISSN: 0028-0836

AB The protein HLA-E is a non-classical major histocompatibility complex (MHC) mol. of limited sequence variability. Its expression on the cell surface is regulated by the binding of peptides derived from the signal sequence of some other MHC class I mols. Here we report the identification of ligands for HLA-E. We constructed **tetramers** in which recombinant **HLA**-E and .beta.2-microglobulin were refolded with an MHC, leader-sequence peptide, biotinylated, and conjugated to phycoerythrin-labeled Extravidin. This **HLA**-E **tetramer** bound to natural killer (NK) cells and a small subset of T cells from peripheral blood. On transfectants, the tetramer bound to the CD94/NKG2A, CD94/NKGK2B and CD94/NKG2C NM cell receptors, but did not bind to the Ig family of NK cell receptors (KIR). Surface expression of HLA-E was enough to protect target cells from lysis by CD94/NKG2A+ NK-cell clones. A subset of HLA class I alleles has been shown to inhibit killing

by CD94/NKG2A+ NK-cell clones. Only the [redacted] alleles that posses a leader peptide capable of upregulating HLA-E surface expression confer resistance to NK-cell-mediated lysis, implying that their action is mediated by HLA-E, the predominant ligand for the NK cell inhibitory receptor CD94/NKG2A.

IT Phycoerythrins
RL: RCT (Reactant)
(Extravidin labeled with; reaction of HLA-E antigen and .beta.2-microglobulin with **HLA** leader peptide in **tetramer** prepn. and)

IT Avidins
RL: RCT (Reactant)
(Extravidin, phycoerythrin-labeled; reaction of HLA-E antigen and .beta.2-microglobulin with **HLA** leader peptide in **tetramer** prepn. and)

IT .beta.2-Microglobulins
RL: RCT (Reactant)
(reaction of HLA-E antigen and .beta.2-microglobulin with **HLA** leader peptide in **tetramer** prepn.)

IT Biotinylation
(reaction of HLA-E antigen and .beta.2-microglobulin with **HLA** leader peptide in **tetramer** prepn. and)

IT 202657-59-8 202657-60-1 202657-61-2 202657-62-3 202657-64-5 205491-11-8
RL: RCT (Reactant)
(reaction of HLA-E antigen and .beta.2-microglobulin with **HLA** leader peptide in **tetramer** prepn.)

L5 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:642784 CAPLUS
DOCUMENT NUMBER: 130:23840
TITLE: A clustered subset of MHC class II molecules
AUTHOR(S): Horejsi, Vaclav; Drbal, Karel; Angelisova, Pavla
CORPORATE SOURCE: Inst. Molecular Genetics, Academy Sciences Czech Republic, Videnska, 1083, Czech Rep.
SOURCE: Immunol. Today (**1998**), 19(10), 486
CODEN: IMTOD8; ISSN: 0167-4919
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Evidence is presented that the clustered subset of MHC class II antigen present in the tetraspan complexes (with CD37, CD53, CD81, CD82) and specifically reactive with CD278 monoclonal antibodies may be identical to the pre-formed **MHC class II** superdimers (**tetramers**). The clustered subset of MHC class II mols. stabilized by interactions with tetraspan proteins may have unique antigen-presenting and signalling properties.

REFERENCE COUNT: 6
REFERENCE(S):
(1) Angelisova, P; Immunogenetis 1994, V39, P249 CAPLUS
(2) Cherry, R; J Cell Biol 1998, V140, P71 CAPLUS
(3) Marks, M; J Biol Chem 1995, V270, P10475 CAPLUS
(4) Rasmussen, A; Eur J Immunol 1997, V27, P3206 CAPLUS
(5) Szollosi, J; J Immunol 1996, V157, P2939 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Immunol. Today (**1998**), 19(10), 486
CODEN: IMTOD8; ISSN: 0167-4919
AB Evidence is presented that the clustered subset of MHC class II antigen present in the tetraspan complexes (with CD37, CD53, CD81, CD82) and specifically reactive with CD278 monoclonal antibodies may be identical to the pre-formed **MHC class II** superdimers (**tetramers**). The clustered subset of MHC class II mols. stabilized by interactions with tetraspan proteins may have unique antigen-presenting and signalling properties.

IT CD antigens
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(CD37, class II antigen complexes; clustered subset of **MHC class II** mols. in tetraspan complexes and possible **tetramer** form)

IT CD antigens
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(CD53, class II antigen complexes; clustered subset of **MHC class II** mols. in tetraspan complexes and possible **tetramer** form)

IT CD antigens
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(CD81 and CD82, class II antigen complexes; clustered subset of **MHC class II** mols. in tetraspan complexes and possible **tetramer** form)

IT Antigen presentation
Signal transduction (biological)
(clustered subset of **MHC class II** mols. in tetraspan complexes and possible **tetramer** form in)

IT Polymerization
(tetramerization; clustered subset of **MHC class II** mols. in tetraspan complexes and possible **tetramer** form)

IT Class II MHC antigens
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(tetraspan complexes; clustered subset of **MHC class II** mols. in tetraspan complexes and possible **tetramer** form)

L5 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
ACCESSION NUMBER: 1998:218179 CAPLUS
DOCUMENT NUMBER: 129:3645
TITLE: Direct isolation, phenotyping and cloning of low-frequency antigen-specific cytotoxic T lymphocytes from peripheral blood
AUTHOR(S): Dunbar, P. R.; Ogg, G. S.; Chen, J.; Rust, N.; Van der Bruggen, P.; Cerundolo, V.
CORPORATE SOURCE: Molecular Immunology Group, Institute Molecular Medicine, John Radcliffe Hospital, University Oxford, Oxford, OX3 9DS, UK
SOURCE: Curr. Biol. (**1998**), 8(7), 413-416
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Current Biology Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cytotoxic T lymphocytes (CTLs) play an important role in controlling viral infections and certain tumors, but characterizing specific CTL responses has always been tech. limited. Fluorogenic '**tetramers**' of major histocompatibility complex (**MHC**) class I complexes have been exploited recently to quantify the massive expansion of specific CTLs in human immunodeficiency virus (HIV) infection. Here, we use **MHC** class I complex **tetramers** to isolate low-frequency antigen-specific CTLs directly from human peripheral blood, allowing the simultaneous phenotypic and functional characterization and cloning of these CTLs. We synthesized a **tetramer** that specifically stained human leukocyte antigen (**HLA**)-A2.1-restricted CTL clones recognizing the influenza matrix protein peptide 58-66, matrix 58-66. This tetramer stained between 1 in 1,500 and 1 in 58,000 peripheral blood mononuclear cells (PBMCs) from HLA-A2.1+ individuals. The surface phenotype of these cells could be analyzed by fluorescence-activated cell sorting (FACS), and the cells could be directly sorted into enzyme-linked immunospot (ELISpot) plates, where they released interferon-.gamma. (IFN-.gamma.) within 1 day of antigen exposure. The same population was cloned by FACS, and the specificity of several expanded clones was confirmed. Cloning was greatly simplified and accelerated compared with std. protocols, and was highly efficient. We also used tetramer-based sorting to enrich melanoma-specific CTLs derived from a tumor-infiltrated lymph node. Direct cloning of specific CTLs from peripheral blood can provide important information about immunol. memory, CTL responses against tumor antigens and CTL proliferation and function, and opens up new possibilities for generating CTLs for adoptive immunotherapy.

SO Curr. Biol. (**1998**), 8(7), 413-416
CODEN: CUBLE2; ISSN: 0960-9822

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ST CTL isolation **HLA** peptide **tetramer**

L5 ANSWER 10 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:108188 BIOSIS
DOCUMENT NUMBER: PREV199900108188
TITLE: A **HLA**-A2-PR1 **tetramer** can be used to isolate low-frequency CTL from the peripheral blood of normal donors that selectively lyse leukemia.
AUTHOR(S): Molldrem, J. J. (1); Lee, P. P.; Wang, C.; Champlin, R. E.; Davis, M. M.
CORPORATE SOURCE: (1) Dep. Blood and Marrow Transplantation, Univ. Tex. M. D. Anderson Cancer Cent., Houston, TX USA
SOURCE: Blood, (**Nov. 15, 1998**) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 254A.
Meeting Info.: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998 The American Society of Heamatology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

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SO Blood, (**Nov. 15, 1998**) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 254A.
Meeting Info.: 40th Annual Meeting of the American. . .

IT . . .
blood and lymphatics, immune system

IT Diseases
chronic myeloid leukemia: blood and lymphatic disease, neoplastic disease

IT Chemicals & Biochemicals
HLA-A2-PRI **tetramer**; IL-2 [interleukin-2]

IT Alternate Indexing
Leukemia, Myeloid, Chronic (MeSH)

L5 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 5
ACCESSION NUMBER: 1998:144200 CAPLUS
DOCUMENT NUMBER: 128:269316
TITLE: Counting antigen-specific CD8 T cells: a reevaluation of bystander activation during viral infection
AUTHOR(S): Murali-Krishna, Kaja; Altman, John D.; Suresh, M.; Sourdive, David J. D.; Zajac, Allan J.; Miller, Joseph D.; Slansky, Jill; Ahmed, Rafi
CORPORATE SOURCE: Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA, 30322, USA
SOURCE: Immunity (**1998**), 8(2), 177-187
CODEN: IUNIEH; ISSN: 1074-7613
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Viral infections induce extensive T cell proliferation in vivo, but the specificity of the majority of the responding T cells has not been defined. To address this issue we used **tetramers** of **MHC** class I mols. contg. viral peptides to directly visualize antigen-specific CD8 T cells during acute LCMV infection of mice. Based on tetramer

binding and two sensitive assays measuring interferon-.gamma. prodn. at the single-cell level, we found that 50%-70% of the activated CD8 T cells were LCMV specific (2.times.107 virus-specific cells/spleen). Following viral clearance, antigen-specific CD8 T cell nos. dropped to 106 per spleen and were maintained at this level for the life of the mouse. Upon rechallenge with LCMV, there was rapid expansion of memory T cells, but after infection with the heterologous vaccinia virus there was no detectable change in the nos. of LCMV-specific memory CTL. Therefore, much of the CD8 T cell expansion seen during viral infection represents antigen-specific cells and warrants a revision of our current thinking on the size of the antiviral response.

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CODEN: IUNIEH; ISSN: 1074-7613

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L5 ANSWER 12 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 6
ACCESSION NUMBER: 1998:583380 CAPLUS
DOCUMENT NUMBER: 129:301388
TITLE: Individual variations in the murine T cell response to a specific peptide reflect variability in naive repertoires
AUTHOR(S): Bousso, Philippe; Casrouge, Armanda; Altman, John D.; Haury, Matthias; Kanellopoulos, Jean; Abastado, Jean-Pierre; Kourilsky, Philippe
CORPORATE SOURCE: Unite de Biologie Moleculaire du Gene INSERM U277, Institut Pasteur, Paris, 75015, Fr.
SOURCE: Immunity (1998), 9(2), 169-178
CODEN: IUNIEH; ISSN: 1074-7613
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous studies have analyzed the diversity of T cell responses upon immunization. Little is known, however, about the individual variability of native repertoires and its influence on immune responses. In the present study, T cells specific for a Kd-restricted epitope derived from HLA-A2 were purified from individual immunized mice using **tetramers** of MHC-peptide. Their TCR.beta. chains were sequenced revealing strong biases but large variations in BJ usage and clonal compn. Most importantly, sequence anal. from nonimmunized mice demonstrated the preexistence of a small set of splenic precursors, distinct in each mouse and comprisingless than 200 cells. Therefore, differences in precursor pools appear to be the major source of individual variability in antigen-selected repertoires.

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CODEN: IUNIEH; ISSN: 1074-7613

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L5 ANSWER 13 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 7
ACCESSION NUMBER: 1998:805923 CAPLUS
DOCUMENT NUMBER: 130:208574
TITLE: In vivo dynamics of anti-viral CD8 T cell responses to different epitopes: an evaluation of bystander activation in primary and secondary responses to viral infection
AUTHOR(S): Murali-Krishna, Kaja; Altman, John D.; Suresh, M.; Sourdive, David; Zajac, Allan; Ahmed, Rafi
CORPORATE SOURCE: Emory Vaccine Center and Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA, 30322, USA
SOURCE: Adv. Exp. Med. Biol. (1998), 452(Mechanisms of Lymphocyte Activation and Immune Regulation VII), 123-142
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Viral infections induce extensive T cell proliferation in vivo. However, only a small fraction (1-5%) of the activated T cells have been shown to be virus specific leading to the prevailing notion that most of the T cell expansion represents cytokine-mediated bystander activation and/or cross reactive stimulation of non specific cells. To re-examine this issue we quantitated antigen specific CD8 T cells during acute LCMV infection of mice using three sensitive techniques: (i) intracellular cytokine prodn., (ii) single cell ELISPOT and (iii) direct visualization of antigen specific CD8 T cells by staining with MHC class I **tetramers** + peptide. In contrast to previous ests., we found that 50-70% of the activated CD8 T cells were LCMV specific. This represented .gtoreq. 10,000-fold increase (.apprx.2.times.107 virus specific cells/spleen) in 8 days with the peak expansion occurring between day 3 and 5 during which period virus specific CD8 T cells had an estd. division time of .apprx.8 h. Following viral clearance, the no. of antigen specific CD8 T cells dropped to 1.times.106 per spleen and were maintained at this level for the life of the mouse. Upon rechallenge with LCMV, memory CD8 T cells rapidly proliferated and again comprised >50% of the total CD8 T cells. In contrast, upon challenge with a heterologous virus such as vaccinia, there was no change in the no. of LCMV specific memory

CTL, despite a substantial increase in the no. of activated CD8 T cells. Taken together, these results show that much of the CD8 T cell expansion seen during viral infection represents antigen specific cells.

REFERENCE COUNT: 46

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(5) Asano, M; J Exp Med 1996, V183, P2165 CAPLUS
(7) Borrow, P; J Exp Med 1996, V183, P2129 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Adv. Exp. Med. Biol. (**1998**), 452(Mechanisms of Lymphocyte Activation and Immune Regulation VII), 123-142
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L5 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 8
ACCESSION NUMBER: 1998:457285 CAPLUS
DOCUMENT NUMBER: 129:174418
TITLE: Conserved T cell receptor repertoire in primary and memory CD8 T cell responses to an acute viral infection
AUTHOR(S): Sourdive, David J. D.; Murali-Krishna, Kaja; Altman, John D.; Zajac, Allan J.; Whitmire, Jason K.; Pannetier, Christophe; Kourilsky, Philippe; Evavold, Brian; Sette, Alessandro; Ahmed, Rafi
CORPORATE SOURCE: Emory Vaccine Cent., Rollins Res. Cent., Emory Univ., Atlanta, GA, 30322, USA
SOURCE: J. Exp. Med. (**1998**), 188(1), 71-82
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Viral infections often induce potent CD8 T cell responses that play a key role in antiviral immunity. After viral clearance, the vast majority of the expanded CD8 T cells undergo apoptosis, leaving behind a stable no. of memory cells. The relationship between the CD8 T cells that clear the acute viral infection and the long-lived CD8 memory pool remaining in the individual is not fully understood. To address this issue, we examd. the T cell receptor (TCR) repertoire of virus-specific CD8 T cells in the mouse model of infection with lymphocytic choriomeningitis virus (LCMV) using three approaches: (a) in vivo quant. TCR .beta. chain V segment and complementarity detg. region 3 (CDR3) length repertoire anal. by spectra typing (immunoscope); (b) identification of LCMV-specific CD8 T cells with **MHC** class I **tetramers** contg. viral peptide and contg. with TCR V.beta.-specific antibodies; and (c) functional TCR fingerprinting based on recognition of variant peptides. We compared the repertoire of CD8 T cells responding to acute primary and secondary LCMV infections, together with that of virus-specific memory T cells in immune mice. Our anal. showed that CD8 T cells from several V.beta. families participated in the anti-LCMV response directed to the dominant cytotoxic T lymphocyte (CTL) epitope (NP118-126). However, the bulk (.apprx.70'%) of this CTL response was due to three privileged T cell populations systematically expanding during LCMV infection. Approx. 30% of the response consisted of V.beta.10+ CD8 T cells with a .beta. chain CDR3 length of nine amino acids, and 40% consisted of V.beta.8.1+ (.beta. CDR3 = eight amino acids) and V.beta.8.2+ cells (.beta. CDR3 = six amino acids). Finally, we showed that the TCR repertoire of the primary antiviral CD8 T cell response was similar both structurally and functionally to that of the memory pool and the secondary CD8 T cell effectors. These results suggest a stochastic selection of memory cells from the pool of CD8 T cells activated during primary infection.

SO J. Exp. Med. (**1998**), 188(1), 71-82
CODEN: JEMEAV; ISSN: 0022-1007

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L5 ANSWER 15 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 9
ACCESSION NUMBER: 1997:726764 CAPLUS
DOCUMENT NUMBER: 128:2728
TITLE: The **tetramer** model: a new view of **class II MHC** molecules in antigenic presentation to T cells
AUTHOR(S): Pareja, E.; Tobes, R.; Martin, J.; Nieto, A.
CORPORATE SOURCE: Seccion Biologia Teorica, Subdireccion Investigacion Docencia, Hospital Virgen Nieves, Granada, E-18110, Spain
SOURCE: Tissue Antigens (**1997**), 50(5), 421-428
CODEN: TSANA2; ISSN: 0001-2815
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Crystallog. studies suggest a plausible divalent interaction between T-cell receptor (TCR) and MHC class II mols. In addn., biochem. data suggest that these divalent MHC mols. are preformed at the membrane of the antigen-presenting cell. The **tetramer** model is based on these preformed tetrameric **class II** mols. that can be loaded with identical or different peptides in their 2 grooves. This enables divalent class II mols. to deliver 2 different messages to T cell: (1) a 2-peptide message, in which the tetramer with 2 identical peptides is able to cross-link 2 TCRs triggering full activation of a T cell. At the thymic level the authors propose that this message induces neg. selection; or (2) a 1-peptide message: only 1 of the peptides loaded in the **class II tetramer** is able to interact with that TCR. This message would be involved in triggering partial activation phenomena in mature lymphocytes, whereas in thymocytes this message would mediate pos. selection. Since high concns. of a peptide would favor the load of tetramers with identical peptides, the tetramer could therefore be viewed as a quant.-qual. transducer that would trigger different responses depending on the concn. of antigenic peptides.
TI The **tetramer** model: a new view of **class II MHC** molecules in antigenic presentation to T cells
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CODEN: TSANA2; ISSN: 0001-2815
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ST **tetramer class II MHC** antigen presentation
IT Antigen presentation
Molecular modeling
T cell (lymphocyte)
T cell activation
(**tetramer** model as new view of **class II MHC** mols. in antigenic presentation to T cells)
IT **Class II MHC** antigens
RL: PRP (Properties)
(**tetramer** model as new view of **class II MHC** mols. in antigenic presentation to T cells)

L5 ANSWER 16 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 10
ACCESSION NUMBER: 1997:363435 CAPLUS
DOCUMENT NUMBER: 127:107660
TITLE: Single particle imaging of cell-surface **HLA** -DR **tetramers**
AUTHOR(S): Wilson, Keith M.; Triantafilou, Kathy; Morrison, Ian E. G.; Cherry, Richard J.; Fernandez, Nelson
CORPORATE SOURCE: Dep. Biological and Chemical Sciences, Central Campus, Univ. Essex, Colchester, CO4 3SQ, UK
SOURCE: Biochem. Soc. Trans. (**1997**), 25(2), 360S
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors used single particle imaging to study the state of immunoreceptors, primarily MHC class II mols., expressed on the surface of transfected human fibroblasts. These fibroblasts are transfected with HLA-DR A and B genes and express non-covalently assocd. HLA-DR .alpha. and .beta. chains. The present expts. provide the first clear evidence that tetramers are present on the surface of intact living cells.
TI Single particle imaging of cell-surface **HLA**-DR **tetramers**
SO Biochem. Soc. Trans. (**1997**), 25(2), 360S
CODEN: BCSTB5; ISSN: 0300-5127
ST particle imaging surface **HLA** DR **tetramer**
IT Molecular association
(single particle imaging of cell-surface **HLA**-DR **tetramers**)
IT **Class II MHC** antigens
HLA-DR antigen
RL: ANT (Analyte); BOC (Biological occurrence); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence)
(single particle imaging of cell-surface **HLA**-DR **tetramers**)
IT Imaging
(single particle, fluorescent; single particle imaging of cell-surface **HLA**-DR **tetramers**)

L5 ANSWER 17 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:363423 CAPLUS
DOCUMENT NUMBER: 127:93881

TITLE: The state of aggregation of MHC class II molecules at the cell-surface is temperature dependent
AUTHOR(S): Triantafilou, Kathy; Wilson, Keith M.; Morrison, Ian E. G.; Cherry, Richard J.; Fernandez, Nelson
CORPORATE SOURCE: Dep. Biological and Chemical Sciences, Central Campus, Univ. Essex, Colchester, CO4 3SQ, UK
SOURCE: Biochem. Soc. Trans. (**1997**), 25(2), 358S
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated whether **tetramer** formation by the **MHC class II** mols. can be manipulated in vitro at 20.degree. and 37.degree. using a human fibroblast cell line transfected with HLA-DR .alpha. and .beta. genes and the invariant chain. At physiol. temps. the authors obsd. the formation of tetramers, but they were less in no. compared to the lower temp. Most likely, at any given time, there is a state of equil. between single dimers and **tetramers** of **class II**. Thus, **MHC class II tetramers** exist at the cell surface and they exist at the cell surface in the absence of T cells.
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CODEN: BCSTB5; ISSN: 0300-5127
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ST **MHC class II tetramer** temp
IT **Tetramers**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(formation; state of aggregation of **MHC class II** mols. at cell-surface is temp. dependent)

L5 ANSWER 18 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:567707 CAPLUS
DOCUMENT NUMBER: 127:246694
TITLE: T cell receptor biochemistry, repertoire selection and general features of TCR and Ig structure
AUTHOR(S): Davis, M. M.; Lyons, D. S.; Altman, J. D.; Mcheyzer-Williams, M.; Hampl, J.; Boniface, J. J.; Chien, Y.
CORPORATE SOURCE: Howard Hughes Medical Institute, Beckman Center, Stanford University School of Medicine, Stanford, CA, 94305-5428, USA
SOURCE: Ciba Found. Symp. (**1997**), 204(Molecular Basis of Cellular Defence Mechanisms), 94-104
CODEN: CIBSB4; ISSN: 0300-5208
PUBLISHER: Wiley
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 20 refs. T cell recognition is a central event in the development of most immune responses, whether appropriate or inappropriate (i.e. autoimmune). We are interested in reducing T cell recognition to its most elemental components and relating this to biol. outcome. In a model system involving a cytochrome c-specific I-Ek restricted T cell receptor (TCR) derived from the 2B4 hybridoma, we have studied the interaction of sol. TCR and sol. peptide-MHC complexes using surface plasmon resonance. We find a striking continuum in which biol. activity correlates best with the dissocn. rate of the TCR from the peptide-MHC complex. In particular, we have found that weak agonists have significantly faster off-rates than strong agonists and that antagonists have even faster off-rates. This suggests that the stability of TCR binding to a given ligand is critically important with respect to whether the T cell is stimulated, inhibited or remains indifferent. It also suggests that the phenomenon of peptide antagonists might be explained purely by kinetic models and that conformation, either inter- or intramol., may not be a factor. We have also studied TCR repertoire selection during the establishment of a cytochrome c response, initially using an anti-TCR antibody strategy, but more recently using peptide-**MHC tetramers** as antigen-specific staining reagents. These **tetramers** work well with either class I or **class II MHC**-specific TCRs and have many possible applications. Lastly, we have also tried to correlate the structural and genetic features of TCRs with their function. Recent data on TCR structure as well as previous findings with antibodies suggest that both mols. are highly dependent on CDR3 length and sequence variation to form specific contacts with antigens. This suggests a general "logic" behind TCR and Ig genetics as it relates to structure and function that helps to explain certain anomalous findings and makes a no. of clear predictions.
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L5 ANSWER 19 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 11
ACCESSION NUMBER: 1998:73086 CAPLUS
DOCUMENT NUMBER: 128:191348
TITLE: Optimization of a peptide-based protocol employing IL-7 for in vitro restimulation of human cytotoxic T lymphocyte precursors
AUTHOR(S): Lalvani, Ajit; Dong, Tao; Ogg, Graham; Pathan, Ansar A.; Newell, Heidi; Hill, Adrian V. S.; McMichael, Andrew J.; Rowland-Jones, Sarah
CORPORATE SOURCE: Institute of Molecular Medicine, Molecular Immunology Group, University of Oxford, Oxford, OX3 9DU, UK
SOURCE: J. Immunol. Methods (1997), 210(1), 65-77
CODEN: JIMMBG; ISSN: 0022-1759
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A variety of different methods for the in vitro restimulation of human cytotoxic T lymphocyte (CTL) precursors (CTLp) are in use. The authors' aim was to enhance the detection of circulating human CTLp in peripheral blood. The authors have developed a standardized and highly efficient method for restimulating CTLp. Synthetic peptides were used to restimulate cognate CTLp from peripheral blood mononuclear cells (PBMC), and effector CTL capable of lysing peptide-pulsed and virus infected targets were generated. The effects of several parameters on CTL specific for influenza A, EBV and HIV-1 were evaluated, and the optimum peptide concn. for CTL generation was established. Supplementation of initial cultures with IL-7 greatly enhanced peptide-specific lytic activity for all peptides tested and the dose-response relation for IL-7 was delineated. A novel technique using peptide-MHC class I mol. **tetramers** to stain T cells bearing cognate T cell receptors permitted enumeration of antigen-specific CD8+ CTL during in vitro restimulation; IL-7 supplementation selectively expanded the population of peptide-specific CD8+ CTL. Importantly, this protocol, while enhancing the restimulation and lytic activity of secondary CTL, does not induce primary CTL in vitro. The improved efficiency with which CTL are generated in this system substantially enhances the sensitivity of CTL culture and the 51Cr release assay to detect low levels of CTL activity.
SO J. Immunol. Methods (1997), 210(1), 65-77
CODEN: JIMMBG; ISSN: 0022-1759
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L5 ANSWER 20 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:608417 CAPLUS
DOCUMENT NUMBER: 125:245038
TITLE: Phenotypic analysis of antigen-specific T lymphocytes
AUTHOR(S): Altman, John D.; Moss, Paul A. H.; Goulder, Philip J. R.; Barouch, Dan H.; McHeyzer-Williams, Michael G.; Bell, John I.; McMichael, Andrew J.; Davis, Mark M.
CORPORATE SOURCE: Sch. Medicine, Stanford Univ., Stanford, CA, 94305-5428, USA
SOURCE: Science (Washington, D. C.) (1996), 274(5284), 94-96
CODEN: SCIEAS; ISSN: 0036-8075
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Identification and characterization of antigen-specific T lymphocytes during the course of an immune response is tedious and indirect. To address this problem, the peptide-major histocompatibility complex (MHC) ligand for a given population of T cells was multimerized to make sol. peptide-MHC **tetramers**. Tetramers of human lymphocyte antigen A2 that were complexes with two different human immunodeficiency virus (HIV)-derived peptides or with a peptide derived from influenza A matrix protein bound to peptide-specific cytotoxic T cells in vitro and to T cells from the blood of HIV-infected individuals. In general, tetramer binding correlated well with cytotoxicity assays. This approach should be useful in the anal. of T cells specific for infectious agents, tumors, and autoantigens.
SO Science (Washington, D. C.) (1996), 274(5284), 94-96
CODEN: SCIEAS; ISSN: 0036-8075
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IT Histocompatibility antigens
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(**HLA**-A2, biotinylated, sol. **tetramers**, complexes with peptides; for phenotypic anal. of antigen-specific T-cells)

L5 ANSWER 21 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:509704 BIOSIS
DOCUMENT NUMBER: PREV199699232060
TITLE: Phenotypic analysis of antigen-specific T lymphocytes.
AUTHOR(S): Altman, John D.; Moss, Paul A. H.; Goulder, Philip J. R.; Barouch, Dan H.; McHeyzer-Williams, Michael G.; Bell, John I.; McMichael, Andrew J.; Davis, Mark M. (1)
CORPORATE SOURCE: (1) Howard Hughes Med. Inst., Dep. Microbiol. Immunol., Beckman Center, Room B221, Stanford Univ., Stanford, CA 94305-5428 USA
SOURCE: Science (Washington D C), (1996) Vol. 275, No. 5284, pp. 94-96.
ISSN: 0036-8075.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Identification and characterization of antigen-specific T lymphocytes during the course of an immune response is tedious and indirect. To address this problem, the peptide-major histocompatability complex (MHC) ligand for a given population of T cells was multimerized to make soluble peptide-**MHC tetramers**. **Tetramers** of human lymphocyte antigen A2 that were complexed with two different human immunodeficiency virus (HIV)-derived peptides or with a peptide derived from influenza A matrix protein bound to peptide-specific cytotoxic T cells in vitro and to T cells from the blood of HIV-infected individuals. In general, tetramer binding correlated well with cytotoxicity assays. This approach should be useful in the analysis of T cells specific for infectious agents, tumors, and autoantigens.
SO Science (Washington D C), (1996) Vol. 275, No. 5284, pp. 94-96.
ISSN: 0036-8075.
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L5 ANSWER 22 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:103106 BIOSIS
DOCUMENT NUMBER: PREV199799402309
TITLE: Single particle imaging of cell-surface **HLA**-DR **tetramers**.
AUTHOR(S): Wilson, Keith M.; Triantafilou, Kathy; Morrison, Ian E. G.; Cherry, Richard J.; Fernandez, Nelson
CORPORATE SOURCE: Dep. Biological Chemical Sci., Central Campus, Univ. Essex, Colchester CO4 3SQ UK
SOURCE: Immunology, (1996) Vol. 89, No. SUPPL. 1, pp. 91.
Meeting Info.: Joint Congress of the British Society for Immunology and the Biochemical Society Harrogate, England, UK December 10-13, 1996
ISSN: 0019-2805.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English
TI Single particle imaging of cell-surface **HLA**-DR **tetramers**
.
SO Immunology, (1996) Vol. 89, No. SUPPL. 1, pp. 91.
Meeting Info.: Joint Congress of the British Society for Immunology and the Biochemical Society Harrogate, England, UK December 10-13, 1996
ISSN: 0019-2805.

L5 ANSWER 23 OF 27 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:389271 CAPLUS
DOCUMENT NUMBER: 125:83729
TITLE: Enumeration and characterization of memory cells in the TH compartment
AUTHOR(S): McHeyzer-Williams, Michael G.; Altman, John D.; Davis, Mark M.
CORPORATE SOURCE: Medical Center, Duke University, Durham, NC, 27710, USA
SOURCE: Immunol. Rev. (**1996**), 150, 5-21
CODEN: IMRED2; ISSN: 0105-2896
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 44 refs. Discussed are: lymphocyte differentiation and repertoire maturation in vivo; the H-2k-restricted pigeon cytochrome C (PCC)-specific response; emergence of a PCC-specific helper T-cell response in TCR transgenic mice; primary and memory PCC-specific helper T-cell response in normal mice; repertoire selection and clonal maturation in the helper T-cell compartment; 5-color flow cytometry for anal. of the developing immune response in vivo; and direct labeling of specific T-cells using peptide/**MHC tetramers**.
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CODEN: IMRED2; ISSN: 0105-2896
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L5 ANSWER 24 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 12
ACCESSION NUMBER: 1995:1001880 CAPLUS
DOCUMENT NUMBER: 124:27586
TITLE: Crystal structure of the V.alpha. domain of a T cell antigen receptor
AUTHOR(S): Fields, Barry A.; Ober, Bertram; Malchiodi, Emilio L.; Lebedeva, Marina I.; Braden, Bradford C.; Ysern, Xavier; Kim, Jin-Kyoo; Shao, Xuguang; Ward, E. Sally; Mariuzza, Roy A.
CORPORATE SOURCE: Cent. Adv. Res. Biotechnol., Univ. Maryland Biotechnol. Inst., Rockville, MD, 20850, USA
SOURCE: Science (Washington, D. C.) (**1995**), 270(5243), 1821-4
CODEN: SCIEAS; ISSN: 0036-8075
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The crystal structure of the V.alpha. domain of a T cell antigen receptor (TCR) was detd. at a resoln. of 2.2 angstroms. This structure represents an Ig topol. set different from those previously described. A switch in a polypeptide strand from one .beta. sheet to the other enables a pair of V.alpha. homodimers to pack together to form a tetramer, such that the

homodimers are parallel to each other and all hypervariable loops face in one direction. On the basis of the obsd. mode of V.alpha. assocn., a model of an (.alpha..beta.)2 TCR **tetramer** can be positioned relative to the major histocompatibility complex **class** II (.alpha..beta.)2 **tetramer** with the third hypervariable loop of V.alpha. over the N-terminal portion of the antigenic peptide and the corresponding loop of V.beta. over its C-terminal residues. TCR dimerization that is mediated by the .alpha. chain may contribute to the coupling of antigen recognition to signal transduction during T cell activation.

SO Science (Washington, D. C.) (**1995**), 270(5243), 1821-4
CODEN: SCIEAS; ISSN: 0036-8075

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L5 ANSWER 25 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 13
ACCESSION NUMBER: 1992:253705 CAPLUS
DOCUMENT NUMBER: 116:253705
TITLE: Tetrameric cell-surface MHC class I molecules
AUTHOR(S): Krishna, Sudhir; Benaroch, Philippe; Pillai, Shiv
CORPORATE SOURCE: Massachusetts Gen. Hosp., Harvard Med. Sch., Boston, MA, 02129, USA
SOURCE: Nature (London) (**1992**), 357(6374), 164-7
CODEN: NATUAS; ISSN: 0028-0836
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purified major histocompatibility complex (MHC) class I mols. have been studied at high resoln. by x-ray crystallog.; the structure is a complex of a single heavy chain, a .beta.2-microglobulin light chain and a tightly bound peptide moiety. Complete **MHC** class I mols. are postranslationally assembled into **tetramers** (made up of 4 heavy chains and 4 .beta.2-microglobulin units), and this tetrameric species is expressed on the cell surface. The multivalent tetrameric structure of class I mols. can be reconciled with models of T-cell activation that invoke antigen-receptor crosslinking, as opposed to models that depend on an allosteric change.

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CODEN: NATUAS; ISSN: 0028-0836

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L5 ANSWER 26 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 79143315 EMBASE
DOCUMENT NUMBER: 1979143315
TITLE: Distribution of class-I and class-II D-fructose 1,6-biphosphate aldolases in various staphylococci, peptococci and micrococci.
AUTHOR: Goetz F.; Nuernberger E.; Schleifer K.H.
CORPORATE SOURCE: Lehrst. Mikrobiol., Techn. Univ., D-8000 Munchen, Germany
SOURCE: FEMS Microbiology Letters, (**1979**) 5/4 (253-257).
CODEN: FMLED7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 004 Microbiology
LANGUAGE: English

AB There are two forms of D-fructose-1,6-bisphosphate aldolases (EC 4.1.2.13) which can be distinguished on the basis of their catalytic and structural properties. Class I aldolases are thought to be typical for higher animals and plants. They consist of **tetramers** with a molecular weight of about 160 000. **Class II** aldolases contain an essential divalent cation, such as Zn2+, Ca2+ or Fe2+, and can be inhibited by 0.01 M EDTA; they have been found in bacteria, fungi and cyanobacteria. As it was thought that class I aldolases were restricted to higher eukaryotic organisms, it was surprising to find a class I aldolase in various strains of staphylococci. This paper describes properties of fructose-1,6-P2 aldolases from micrococci, staphylococci and peptococci. The micrococci possess, like most bacteria, a class II aldolase. This aldolase can easily be identified by its sensitivity to EDTA. Furthermore the micrococcal aldolase is activated by K+ ions and is not inhibited by NaBH4 and dihydroxy-acetone-P treatment. The electrophoretic mobility of the micrococcal aldolases is, because of its slower migration rate, clearly distinct from the staphylococcal and peptococcal aldolases. In the latter organisms only a class I type aldolase was found. A comparison of the aldolases from staphylococci and peptococci with the well investigated aldolase from P. aerogenes exhibited very similar properties. Slight differences between the aldolases of these two groups of bacteria were only found in regard to the electrophoretic mobility. The class I type aldolases of staphylococci and peptococci differ from those of higher animals and plants by their insensitivity to carboxypeptidase A and their completely different electrophoretic mobility.

SO FEMS Microbiology Letters, (**1979**) 5/4 (253-257).
CODEN: FMLED7

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L5 ANSWER 27 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 14
ACCESSION NUMBER: 1978:575668 CAPLUS
DOCUMENT NUMBER: 89:175668

TITLE: Mechanism of pigeon liver malic enzyme. Reactivity of class II sulfhydryl groups as conformational probe for the "half-of-the-sites" reactivity of the enzyme with bromopyruvate

AUTHOR(S): Pry, Terry A.; Hsu, Robert Y.
CORPORATE SOURCE: Upstate Med. Cent., State Univ. New York, Syracuse, N. Y., USA

SOURCE: Biochemistry (1978), 17(19), 4024-9
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A method is described for the selective masking of nonessential SH groups of pigeon liver malic enzyme by 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB) and N-ethylmaleimide (NEM) in the presence of NADP, Mn2+, and the substrate analog, tartronate. The resulting enzyme deriv. contg. 4 intact **class II** SH groups/**tetramer** is fully active in the oxidative decarboxylation of malate. Alkylation of 2 class II SH groups by the affinity label, bromopyruvate, inactivates this enzyme and abolishes the reactivity of the 2 remaining groups toward this reagent, confirming the half-of-the-sites behavior reported in a previous communication. In contrast, all-of-the-sites reactivity is obtained for DTNB, NEM, iodoacetate, and iodoacetamide, which cause inactivation by reacting with all of the class II SH groups. The reaction of the enzyme deriv. with DTNB or NEM follows a pseudo-1st-order process, yielding 2nd-order rate consts. of 0.49 and 0.13 mM-1 min-1, resp. The rate const. of DTNB is unaffected by partial modification of the enzyme with other all-of-the-sites reagents, whereas the rate consts. of both reagents with enzyme which has been exhaustively alkylated by bromopyruvate are decreased by 2.4-fold for DTNB and 3.6-fold for NEM. The reaction of partially alkylated malic enzyme contg. <2 bound pyruvyl residues/tetramer exhibited biphasic behavior which can be accounted for by 2 parallel pseudo-1st-order processes with rate consts. corresponding to those of the unalkylated and dialkylated enzyme. The half-of-the-sites effect of bromopyruvate is interpreted on the basis of neg. cooperativity resulting from specific conformation changes induced by the alkylating ligand.

SO Biochemistry (1978), 17(19), 4024-9
CODEN: BICHAW; ISSN: 0006-2960
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